The American Journal of Medicine

March 1950

The American Journal of Medicine

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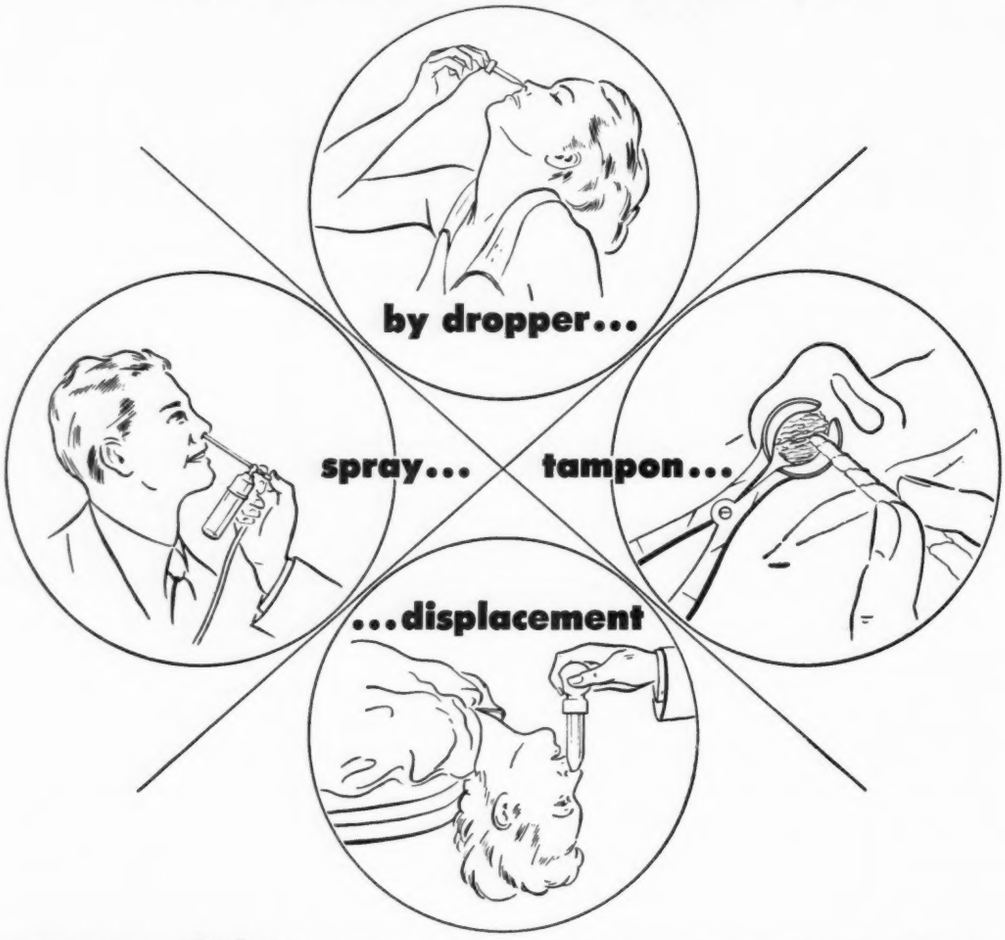

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Editorial

Clinical Studies

This detailed metabolic study of the effects of ACTH in a case of long-standing hypopituitarism disclosed no response in carbohydrate or nitrogen metabolism whereas typical electrolyte and other responses were elicited. This suggests that atrophy of some but not all adrenal cortical secretory elements was present. A comparison is also made of the effects of ACTH in primary myxedema before and after thyroid medication.

This paper describes experience with prepared insulin mixtures in 185 patients observed under normal living conditions in office practice. NPH 50 proved adequate in 40 per cent of the patients, the remainder required various mixtures conveniently prepared in oversized vials.

An interesting study of the effects of diabetes mellitus on the liver based on observations in 380 diabetics.

The authors have compared the results of clinical, laboratory and liver biopsy estimates of the severity of hepatic disease in sixty-two cases of Laennec's cirrhosis of the liver and are impressed with the limitations in interpretation of liver biopsies. This experience does not diminish the usefulness of needle biopsies but emphasizes the need of integration of all the data available for interpretation and prognosis.

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By definition

clinically, ***hydrocholeresis*** might well be defined as "the therapeutic effect produced by *Decholin Sodium* (brand of sodium dehydrocholate)," so specifically is this pure bile acid derivative identified with the basic experimental and clinical studies on medical management in biliary tract disorders.

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Sulfamethazine

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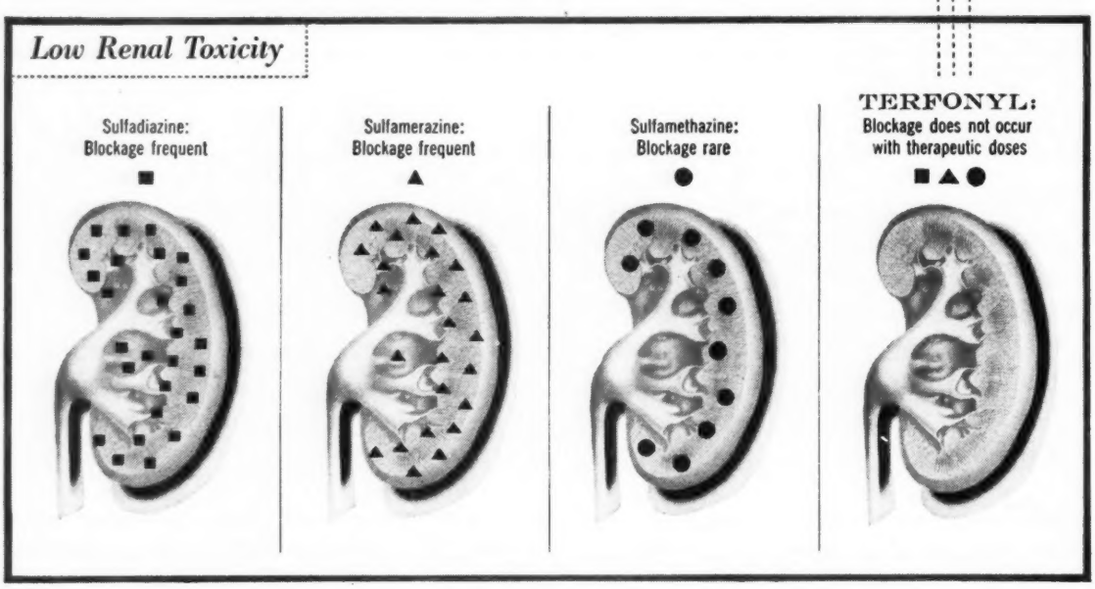

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Special Feature

Case Report

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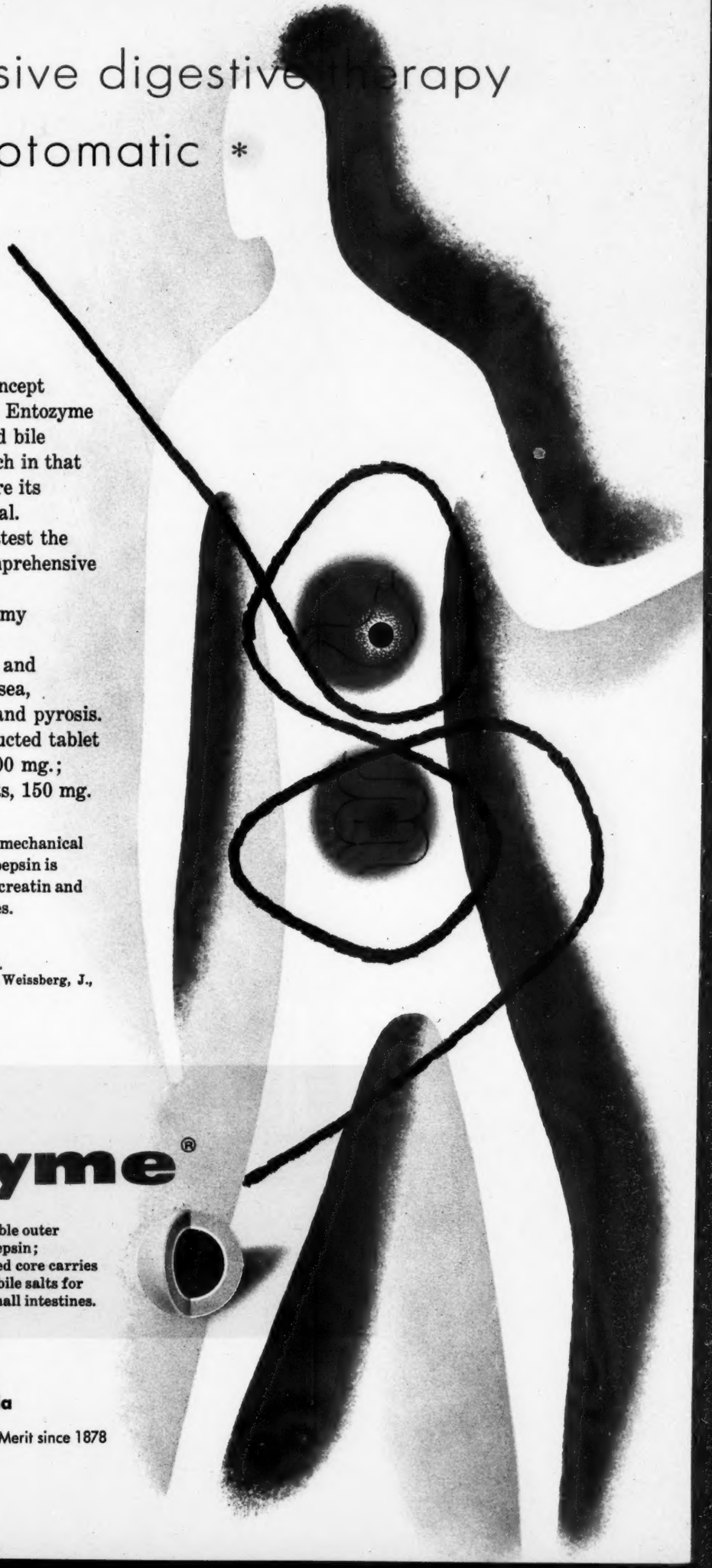

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1. McGavack, T. H., and Klotz, S. D.: Bull. Flower Fifth Ave. Hosp., 9: 61, 1946. 2. Weissberg, J., et al.: Am. J. Digest Dis., 15: 332, 1948.

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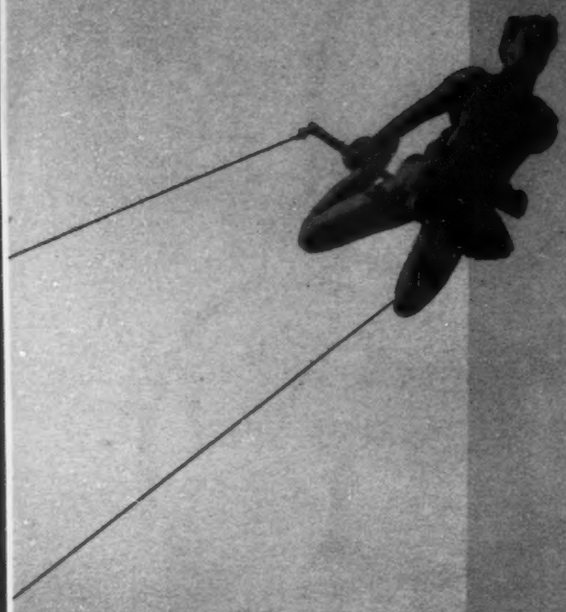

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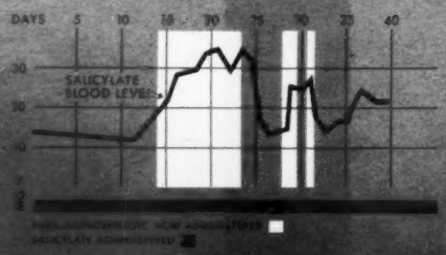

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References
1. Dorfman, A., et al.: Proc. Soc. Exper. Biol. and Med., 64: 357, 1947.
2. Dry, T.J.: Proc. Central Soc. Clin. Research, 19: 69, 1946.
3. Rosenblum, I. and Fraser, L. E.: Proc. Soc. Exper. Biol. and Med., 65: 178, 1947.

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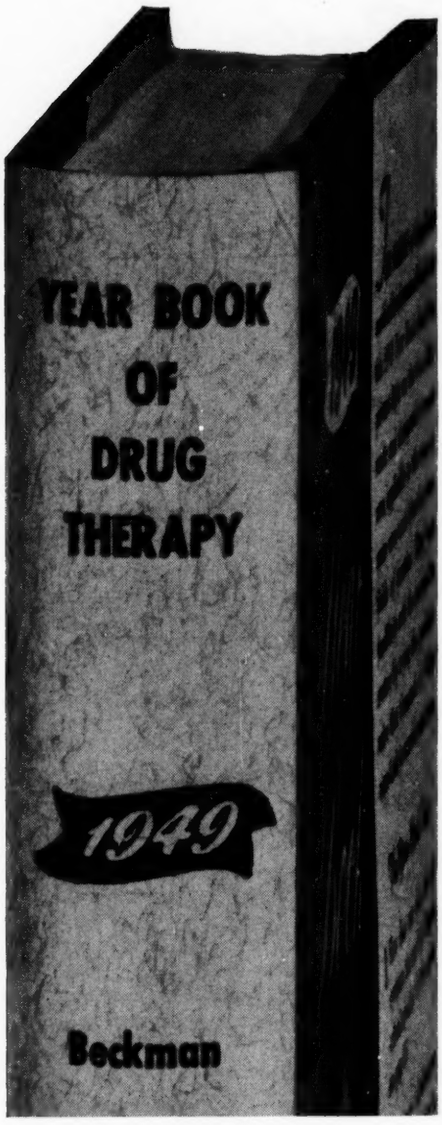

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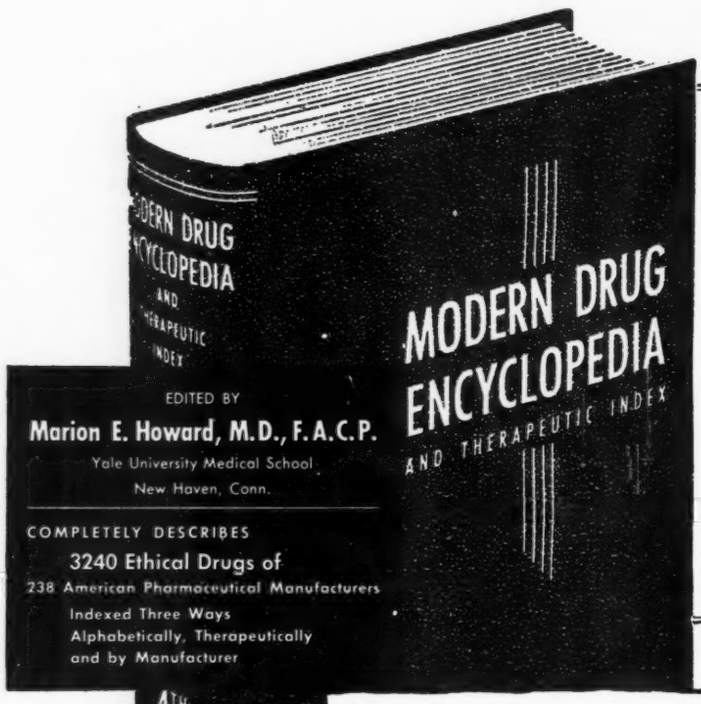

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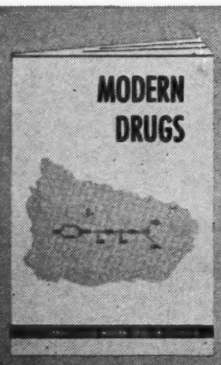

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1. Phillips, W. F. P., and Fishbein, W. I.: Indust. Med. & Surg. *18*:526 (Dec.) 1949

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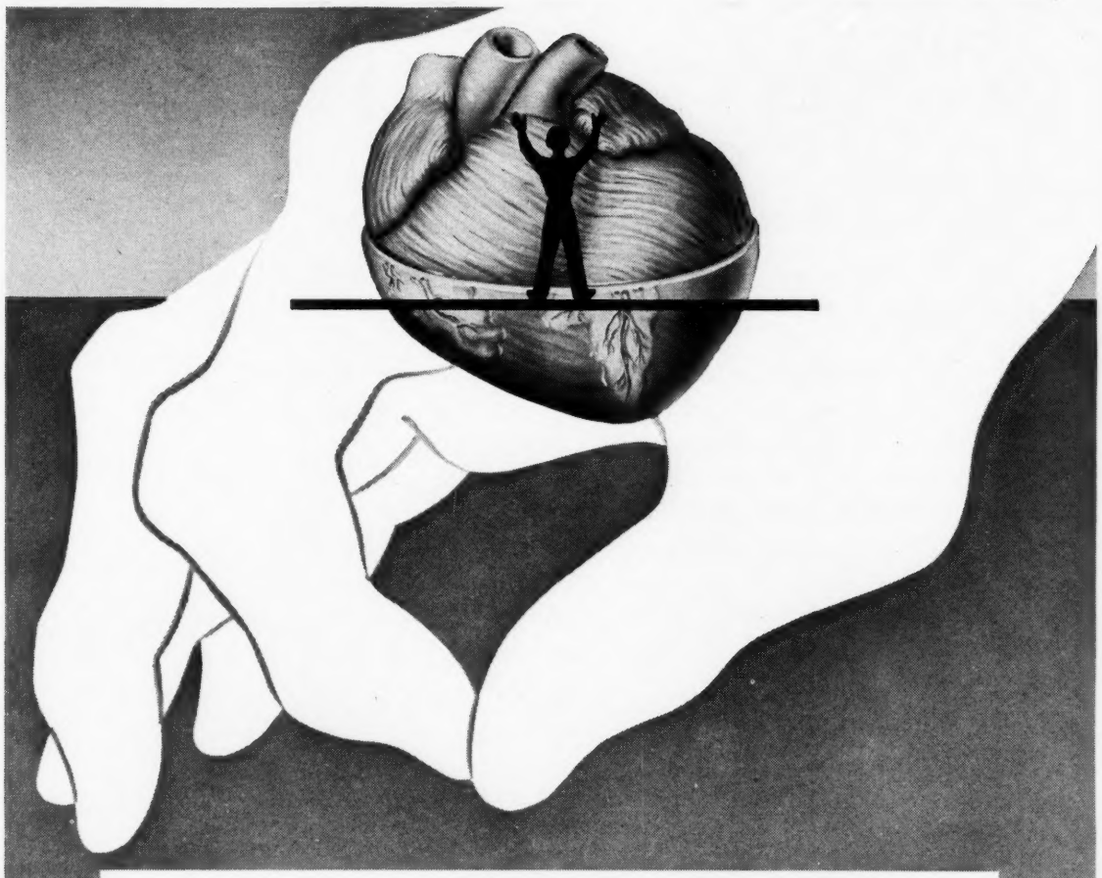

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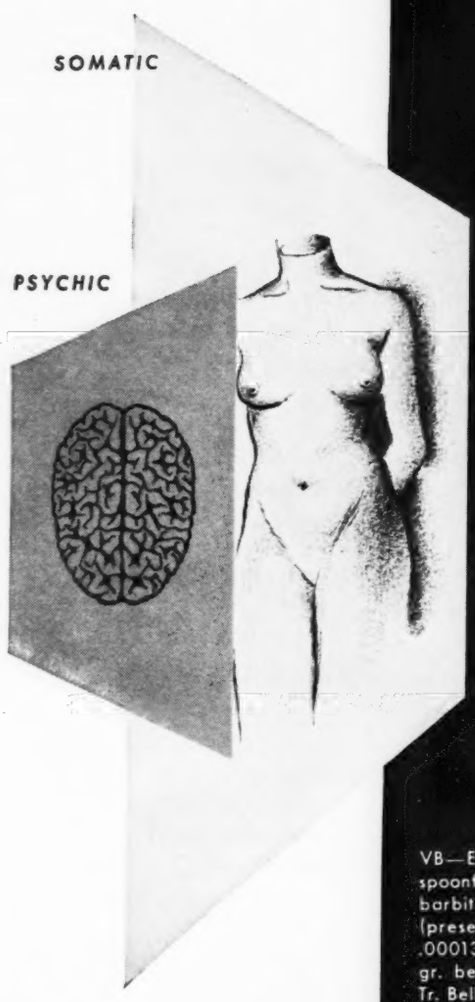

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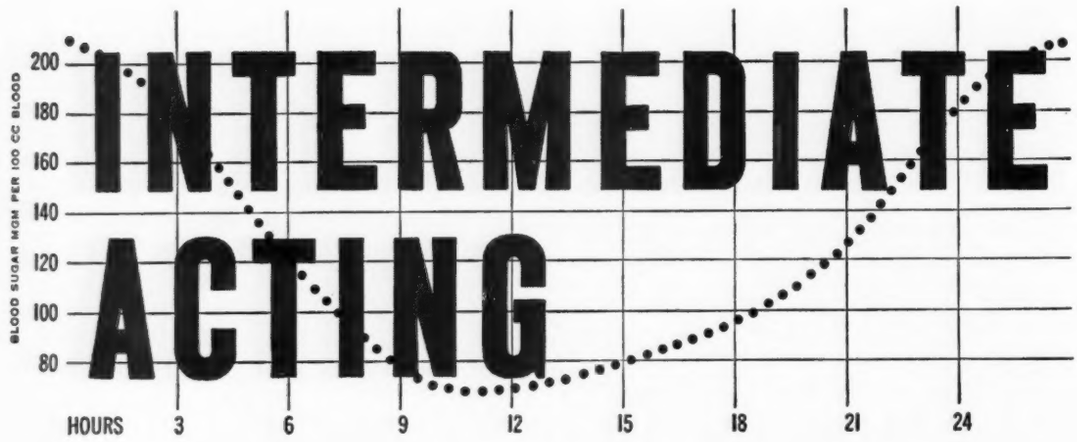

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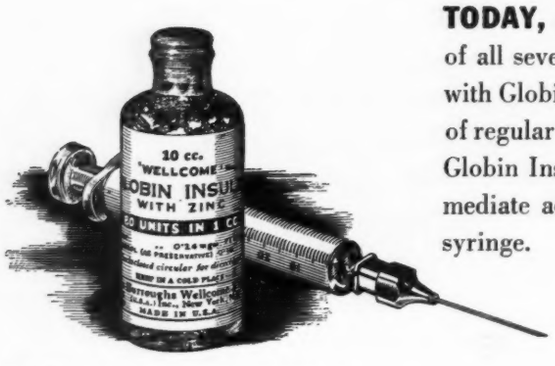

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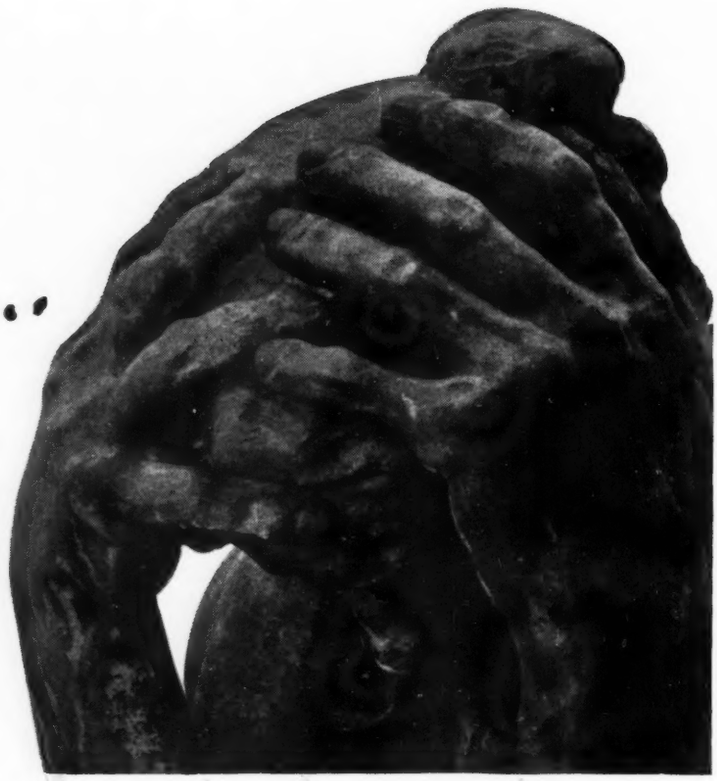

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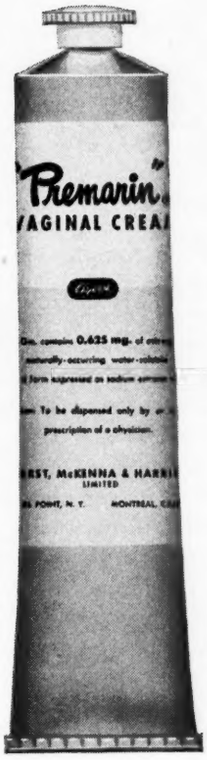

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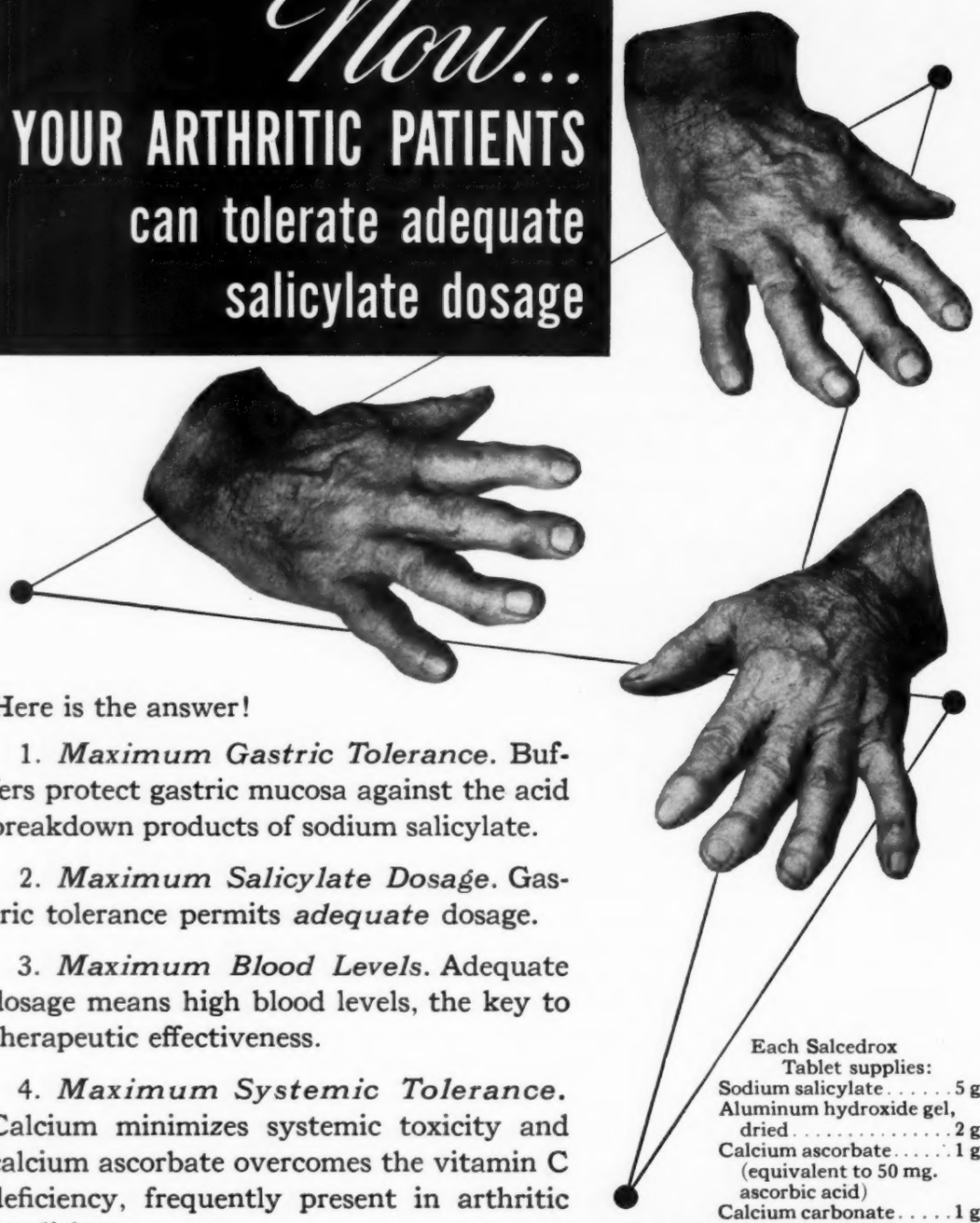

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DOSAGE: Adults: 1 to 2 teaspoonfuls, repeated every 2 to 3 hours as necessary. Children: ½ to 1 teaspoonful according to age, 3 or more times daily.

SUPPLIED: In pints and gallons.

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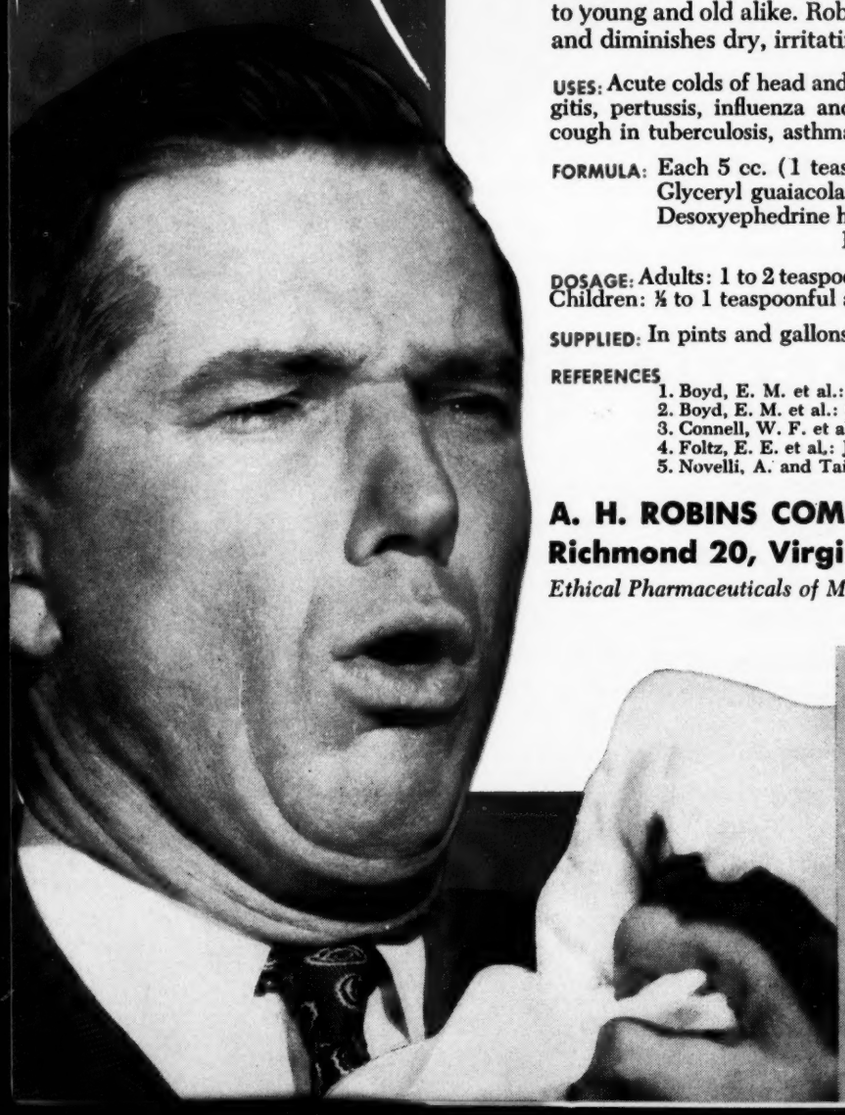

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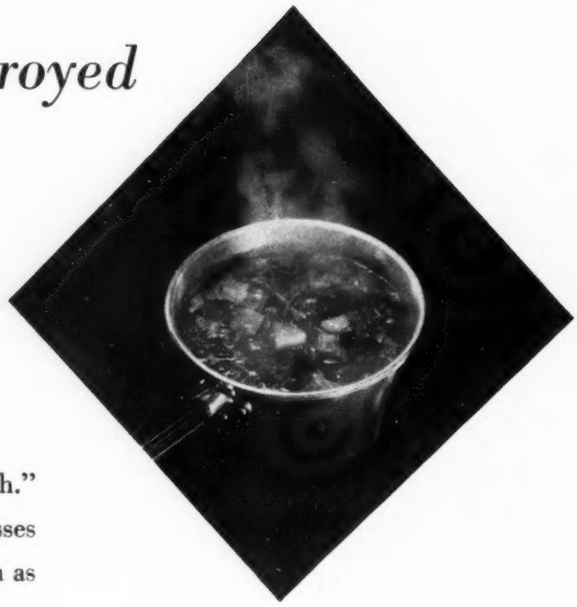

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The American Journal of Medicine

VOL. VIII MARCH, 1950 No. 3

Editorial

Relation of Acute Hepatitis to Cirrhosis of the Liver

THE ultimate course of patients with signs of protracted viral hepatitis has been a subject of interest and concern. It seems fairly certain that the majority of patients with mild, persistent symptoms, whose liver biopsies show moderate periportal inflammation with slight fibrosis, will recover completely. However, there remain a few who show signs of progressive deterioration and die of cirrhosis which has been described as of various types. The literature on this subject is confusing because the classification of cirrhosis is not agreed upon by clinicians or pathologists. Three types of cirrhosis have been described as sequellae to viral hepatitis: (1) post-necrotic, (2) cholangiolitic and (3) Laennec's. It seems unlikely that all three types have a common etiology.

Post-necrotic or coarsely nodular cirrhosis differs from subacute yellow atrophy only in the longer time interval from the initial hepatitis to the stage of liver failure. Whereas subacute yellow atrophy generally runs a fatal course within a few weeks or months, the identical pathologic findings have been seen in patients surviving years after the initial hepatitis. The writer has observed fifteen cases (seven proved, eight presumptive) with survival from six months to thirteen years after the onset of the illness. The disease was latent or unrecognized in several of these cases before signs of liver failure appeared. Once failure occurred there was a progressive downhill course. The fact that the pathologic features of post-necrotic cirrhosis remained true to type even though the initial hepatitis took place years before suggests that there is no tendency for this type to develop into the Laennec type of disease. The development of post-necrotic cirrhosis bears no relation to the severity of the initial attack. This suggests either that the virus may remain active in these patients or that some other process prevents the resolution and repair of the acute hepatitis.

Another form of cirrhosis that is being seen more frequently than in the past is cholangiolitic or hypertrophic biliary cirrhosis. In these patients intermittent fever, jaundice, pronounced hepatosplenomegaly and abdominal discomfort usually continue for years before the onset of failure. Laboratory tests suggest extrahepatic biliary obstruction because of increased serum cholesterol and alkaline phosphatase, and frequently a negative cephalin-cholesterol flocculation reaction. The liver cells at first appear to be relatively normal but there is fine intralobular fibrosis and cellular infiltration about the small bile ducts and portal radicles. The fatal termination is characterized by cholemia, at times complicated by hemorrhage or ascites formation. The possibility remains that this is a separate entity. The clinical features and pathology are peculiar. They recall certain

cases of sensitivity to arsenicals in which intrahepatic biliary tract obstruction has been described. Is it possible that cholangiolitic cirrhosis represents a chronic sensitivity reaction primarily within the smallest bile radicles with subsequent changes in the liver cells?

In most reported series of Laennec's cirrhosis the incidence of ancient jaundice has varied from 7 to 13 per cent. However, in a more recent series 33 per cent of the patients gave a story of antecedent jaundice as compared to 7 per cent of a control hospital population. The question properly was raised as to whether infectious hepatitis may have led to Laennec's cirrhosis in these cases. The explanation is not clear. It is conceivable that patients with subclinical Laennec's cirrhosis are more susceptible to intercurrent hepatitis than the general population.

In reports on puncture biopsies of the liver cirrhotic changes have been described as a sequel to acute hepatitis. From the small sections obtained it is not always possible to define these positively as Laennec's cirrhosis. The cases have been few and the likelihood exists in certain instances that cirrhosis may have antedated the episode of acute hepatitis. At the present time there seems to be insufficient evidence to indicate that infectious hepatitis *per se* leads to Laennec's cirrhosis.

ARTHUR J. PATEK, JR., M.D.
Columbia Research Service
Goldwater Memorial Hospital, N. Y.

Clinical Studies

Effects of Pituitary Adrenocorticotrophic Hormone (ACTH) in Panhypopituitarism of Long-standing and in Myxedema*

ABBIE I. KNOWLTON, M.D., JOSEPH W. JAILER, M.D., HOWARD HAMILTON, M.D. *and* RANDOLPH WEST, M.D.†

New York, New York

WITHIN the past two years sufficient amounts of pituitary adrenocorticotrophic hormone (ACTH) have become available to permit observations in human subjects. From these studies it is evident that the administration of this pituitary hormone to normal individuals results in an increase in adrenal activity: sodium retention with potassium diuresis,[2,3,4] decreased carbohydrate tolerance and negative nitrogen balance with increased urinary excretion of "corticoids"[1–7] and an augmented excretion of 17-ketosteroids in the urine.[1–3,5–7] In addition, ACTH administration has been accompanied by a striking fall in circulating eosinophiles[2,6,7] and increased uric acid excretion in the urine.[2,3,6,7]

In animals following extirpation of the pituitary, ACTH will prevent the adrenal atrophy which characteristically ensues[8] and in addition will cause regeneration of the adrenals after atrophy has taken place.[9,10] However, it has been shown that much larger quantities of ACTH are required to restore adrenal weight after the posthypophysectomy atrophy has occurred than to maintain adrenal weight after hypophysectomy.[11] Forsham et al.[2] have reported a normal response to stimulation with this pituitary hormone in a human with mild hypopituitarism; however, in patients with severe hypopituitary states, these workers observed a diminished response to a single injection of ACTH. The lack of response in such patients may indicate that the adrenal atrophy is of such extent that the gland is no longer capable of responding to the pituitary hormone. However, the question may also be raised as to whether the associated hypothyroidism in panhypopituitary states may itself alter the ability of the organism to respond to ACTH. Studies in thyroidectomized animals given ACTH have yielded conflicting results. Some reports give evidence that little adrenal enlargement occurs in such animals[12,13,14] while others state that the response in the absence of the thyroid is similar to that in intact animals.[15,16] In the myxedematous patient the findings of decreased excretion of "corticoids"[17] and of low serum sodium values[18] suggest altered adrenal function in this state.

The present study was undertaken first to determine the effect of several days of ACTH administration in a patient with long-standing panhypopituitarism and second to compare the effects of ACTH in a patient with primary myxedema prior to and after institution of thyroid therapy.

EXPERIMENTAL

The patient selected for the study of the effect of ACTH in long-standing hypopituitarism was

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† Died May 20, 1949.

a fifty-one year old housewife, M. M. Eighteen years previously, following her only delivery, there had been severe postpartum bleeding followed by persistent headaches, amenorrhea, progressive loss of body hair and generalized weakness. Hypothyroidism was first diagnosed thirteen years later and for this condition she had been treated intermittently with thyroid extract. On her initial admission to the hospital she was demonstrated to have (1) hypothyroidism (basal metabolic rate, −41 per cent; serum cholesterol, 587 mg. per cent; 24-hour uptake of radioactive iodine by the thyroid gland, 2 per cent of the administered tracer dose, and urinary excretion during this period was 31 per cent of dose given); (2) hypogonadism (amenorrhea); and (3) hypoadrenalism (serum sodium as low as 117.2 mEq./L., with a subsequent rise to normal values during therapy with desoxycorticosterone acetate (DCA) and added sodium chloride, 17-ketosteroid excretion of less than 1 mg. in twenty-four hours. Because of the severity of her disease it was necessary to maintain her on thyroid extract U.S.P. 15 mg. orally and desoxycorticosterone acetate (DCA) 3 mg. subcutaneously daily throughout the experimental period.

The daily diet was calculated to contain 1,900 calories, 232 gm. of carbohydrate, 75 gm. of protein and 75 gm. of fat. An aliquot of the daily diet was subjected to chemical analysis during six of the seven experimental periods. To minimize fluctuations in sodium and chloride intake the diet was prepared as a low sodium diet. Sodium chloride (4 gm.) was added to this daily in a weighed salt shaker. The entire diet and contents of the salt shaker were consumed each day with the exception of the last day. On this day the uneaten food was returned to the laboratory for analysis and this was subtracted from the determined aliquot of the period to arrive at this day's intake. The patient drank only distilled water and fluid intake was maintained at 1,520 cc. daily, with the exception of the twelfth day when an extra 150 cc. was administered.

Twenty-four hour urine specimens were collected daily with 5 cc. of chloroform added as a preservative. The stools for each experimental period were collected as a single specimen without preservation.

At intervals during the study the basal metabolic rate was determined and blood was withdrawn for analysis, with the patient in the fasting state. Four intravenous glucose tolerance tests were performed during the experimental period and on these days the diet and fluid intake were correspondingly reduced. The experimental periods were divided as shown in Table 1. The ACTH was given intramuscularly, freshly dissolved in saline, at six hourly intervals.

The patient selected for the study of the effects of ACTH in hypothyroidism was a fifty-two year old housewife, M. D., whose disease had been present for thirteen years or more. She had never been pregnant; menses had ceased at the age of thirty-nine. She had never received any thyroid medication. For fourteen years or more she had suffered from easy fatiguability and had complained of puffiness around her eyes, and of her hands and legs. Fourteen years prior to entry her physician told her that she had anemia and an enlarged heart. In the seven or eight years before entering the hospital all her symptoms progressed and in addition she noticed slowing of her speech and deepening of her voice, poor muscular coordination and a decrease in axillary hair. The initial work-up confirmed the presence of hypothyroidism, basal metabolic rate, −23 per cent; 24-hour uptake of a tracer dose of radioactive iodine, 0 per cent; serum cholesterol, 426 mg. per cent. Her heart was enlarged as determined by x-ray measurement and her venous pressure was 120 mm. water and minimal ankle edema was noted. Low voltage was present in the electrocardiogram. A moderate anemia was present, hemoglobin 11.8 gm., red blood cells, 3.1 million. X-rays of the skull showed no evidence of enlargement of the sella turcica. The diet employed during the first experimental period contained 1,735 calories, 180 gm. of carbohydrate, 77 gm. protein and 79 gm. fat. The diet was prepared, as for the first patient, salt-poor and 4 gm. of sodium chloride were added to this daily from a weighed salt shaker. The daily fluid intake was maintained at 1,200 cc. of distilled water.

Urine and stool collections were made in the same manner as in the first patient, except that in this patient twenty-four-hour urines were collected without preservative, the specimen kept at icebox temperature during the twenty-four hours and subsequently. Determinations of basal metabolic rate, withdrawal of blood samples and glucose tolerance tests were performed as in the study of the first patient. In addition, eosinophile counts were made during

the control period before and four hours after the injection of whole posterior pituitary extract, before and four hours after the initial injection of ACTH and again on the last four days of ACTH administration. During the initial control period and again on the eighth day of ACTH the twenty-four-hour up-take of radioactive iodine by the thyroid gland was determined.

TABLE I

Period	No. of Days	Lot. No.	Armour Standard (mg. per day)	Posterior Pituitary Oxytoxic (units per day)
Patient M. M. Hypopituitarism ACTH				
I	4			
II	4			
III	5	37 K-E	33	2
IV	5	37 K-E	66	4
V	6			
VI	6			
VII	2	37 K-G	104	5.1
Patient M. D. Myxedema ACTH				
I	4			
II	4			
III	4	G-1112	66–75[1]	3.0
IV	4	G-1112	75	3.0
V	4			
VI	3			
Patient M. D. Myxedema Treated ACTH				
I	3			
II	3			
III	4	H-2303	72	<1
IV	3	H-2303	72	<1
		G-1112[2]	75	3.0
V	4			
VI	4			

[1]—Day 1 of period III: 66 mg.
Day 2 of period III: 70 mg.
Days 3 and 4 of period III: 75 mg.
[2]—Day 1 of period IV: 72 mg. of Lot H-2303
Days 2 and 3 of period IV: 75 mg. of Lot G-1112

The experimental periods were divided as shown in Table I. During two days of the initial control periods the patient was given whole posterior pituitary extract at six hourly intervals in amounts calculated to approximate that present in the ACTH employed. The ACTH was administered as in the first patient.

After completion of the study thyroid medication was instituted. The patient exhibited a dramatic response, her myxedematous appearance disappeared and a 7 kg. weight loss ensued. Three months later when the patient appeared to be euthyroid, she returned to the hospital for a second period of study. Throughout this experimental period her daily dosage of thyroid U.S.P. 60 mg. was continued. The plan of this study, as nearly as possible, duplicated that for patient, M. M. The diet was calculated to contain 1,752 calories, 186 gm. of carbohydrate, 77 gm. of protein and 78 gm. of fat. It was prepared similarly to the previous diet. The daily fluid intake was, as previously, 1,200 cc. In this study eosinophile counts were made before and four hours after the initial injection of ACTH. No determinations of radioactive iodine up-take were made.

The experimental period, were divided as shown in Table I. Posterior pituitary in doses comparable to that contained in the ACTH employed was given intramuscularly at six-hour intervals during two days of the initial control periods and again for two days in the final control period.

METHODS

Sodium and potassium determinations on serum, urine, stool and diet specimens were made with an internal standard flame photometer having an accuracy of 1 per cent.[19] Chloride analyses on all specimens were made according to Wilson and Ball's[20] modification of Van Slyke's method.[20] Calcium was determined as outlined by Kramer and Tisdall,[22,23] while in urine, stool and diet analyses the method of Sendroy[24] with modifications introduced by B. B. Markardt (unpublished data) was used. Bodansky's method[25] was followed for determining serum phosphorus and the colorimetric method of Fiske and Subbarow[26] was employed for phosphorus determinations on urine, stool and dietary specimens. Serum urea nitrogen determinations were made as outlined by Gentzkow.[27] Nitrogen in urine and stool specimens were determined by micro-Kjeldahl. Benedict's method[22] was followed in serum uric acid analyses while in urine samples that of

Christman and Ravwitch[29] was employed. Serum cholesterol values were obtained by the Schoenheimer-Sperry[30] technic, with modifications introduced by Bodansky.[31] Carbon dioxide content was determined by the method of van Slyke. Total proteins were estimated according to Lowry and Hunter[32] and the Folin modification of the Folin-Wu method was employed for blood sugars.[33,34] Urinary creatine and creatinine values were read in a photoelectric colorimeter, following Peters' method.[35] Estrogens (estrone plus estradiol) were determined by the method of Jailer[36] and 17-ketosteroids with dinitrobenzene as described by Holtorff and Koch.[37] Formaldehyde-liberating steroids, presumably 11-oxysteroids, or "corticoids" were estimated by the method of Daughaday, Jaffe and Williams.[38] Intravenous glucose tolerance tests were made according to the technic outlined by Thorn et al.[39] and eosinophile counts according to the method described by Forsham et al.[2]

RESULTS

1. The patient with hypopituitarism, M. M., remained well until the final day of this study (the second day of period VII, ACTH 104 mg.). She then complained of abdominal cramps, anoxia and such discomfort that the study was terminated.

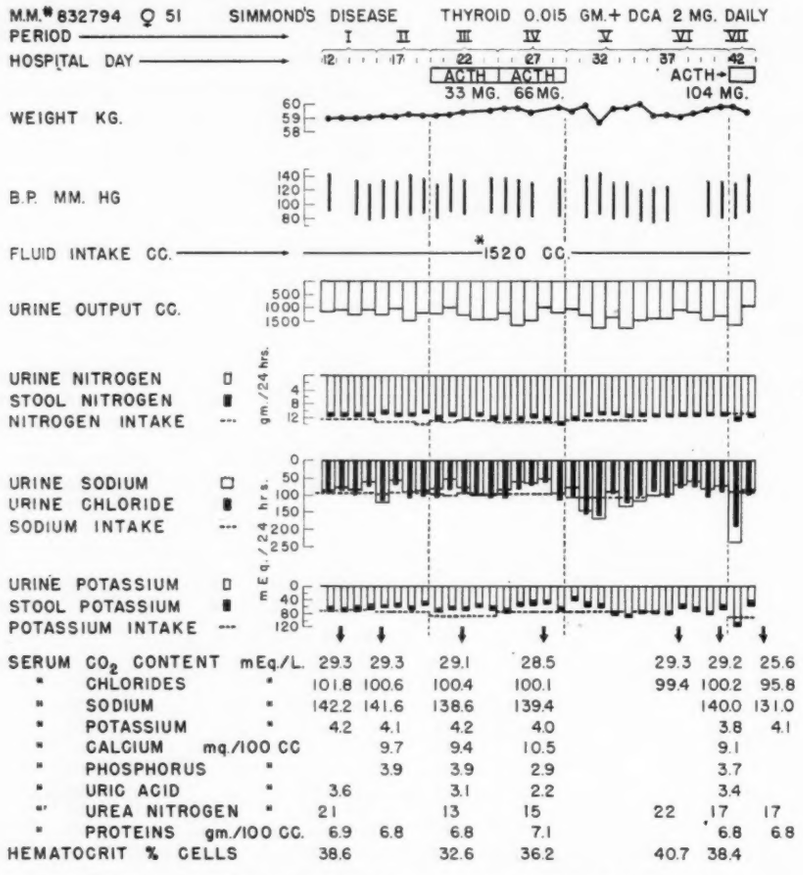


FIG. 1.

Electrolyte and Mineral Metabolism (Table II and Fig. 1). There was a slight retention of sodium in the period during which the patient received 66 mg. daily (an average daily balance of +21.6 mEq. as compared with +11.3 and +1.6 during the two initial control periods). Following withdrawal of the hormone there was a definite diuresis of sodium. The chloride balance followed the pattern of sodium but the changes were less decisive. In neither sodium nor chloride were the urinary changes accompanied by a fluctuation in

serum values. In the final period of ACTH administration (104 mg. daily, period VIII) a striking diuresis of sodium and chloride and drop in serum levels of these substances occurred for reasons wholly unexplained and contrary to the usual findings.

There was no significant alteration in the excretion of potassium and the serum level remained unaltered during the first two periods of ACTH. Following subsidence of sodium diuresis which occurred the second and third days after ACTH withdrawal there ensued three days during which the patient was in negative potassium balance. In the final period of ACTH administration a marked potassium diuresis occurred.

Not included, for the sake of space conservations, are the balance data on calcium and phosphorus. No increased excretion of calcium occurred during ACTH administration. Serum levels of calcium remained within normal limits throughout the study although there was a minimal and questionably significant rise observed during the period of ACTH injections.

There was no alteration in phosphorus excretion. There was a single unexplained observation of a decrease in serum level during ACTH administration. No increase in serum bicarbonate content was noted during the period of hormone injections.

Protein Metabolism (Table II, Fig. 1). ACTH did not cause increased nitrogen excretion in this patient. The fall in serum urea nitrogen levels during ACTH injections is of questionable significance. The serum uric acid did decrease somewhat during ACTH administration and there was a 20 per cent increase in uric acid excretion while the patient was receiving 66 mg. ACTH daily. Creatine excretion fluctuated widely throughout the study. Creatinine excretion remained constant throughout the entire period of observation with the exception of one day during control period V.

17-Ketosteroid and Estrogen Excretion (Table II). Administration of ACTH resulted in a definite increase in the excretion of 17-ketosteroids from the extremely low control values which ranged from 0.67 to 0.99 mg. per day to a peak of 2.56 mg. while the patient was receiving ACTH. There was no corresponding increase in estrogen excretion. Following withdrawal of ACTH the 17-ketosteroid excretion decreased, returning to the range of pre-injection control values in six days.

Carbohydrate Metabolism (Fig. 4). The fasting blood sugars, determined after three days of ACTH (33 mg. daily) and again after seven days of ACTH (33 mg. daily for five days, 66 mg. daily for two days), were similar to the control value. The results of intravenous glucose tolerance tests done at these times (i.e., after three days of ACTH 33 mg. daily and after seven days of ACTH) showed no decrease in glucose tolerance and were similar in character to those obtained in the control period.

Basal Metabolism. A progressive and significant increase in the basal metabolic rate occurred during the ACTH periods (Table V), with a return to previous low values after the hormone injections were stopped. Changes in serum cholesterol (Table V) were less impressive but the lowest value was obtained while the patient was receiving 66 mg. daily of ACTH, and ten days after withdrawal of the hormone the cholesterol value had risen significantly. These changes are of particular interest since this preparation of ACTH on assay was found to contain negligible amounts of thyrotropic hormone.

II. ***Patient M. D. Myxedema, before and after Thyroid Replacement Therapy.*** The determinations made upon this patient are presented in graphic form in Figures 2 and 3, and the balance data in Tables III and IV.

In the study performed before thyroid therapy was started, the patient, during the administration of ACTH, became increasingly uncomfortable due to fluid retention. Her weight increased 3 kg. and dependent edema became more marked. It is of interest that a similar rate of gain obtained during the two days of the initial control periods, during which whole posterior pituitary ex-

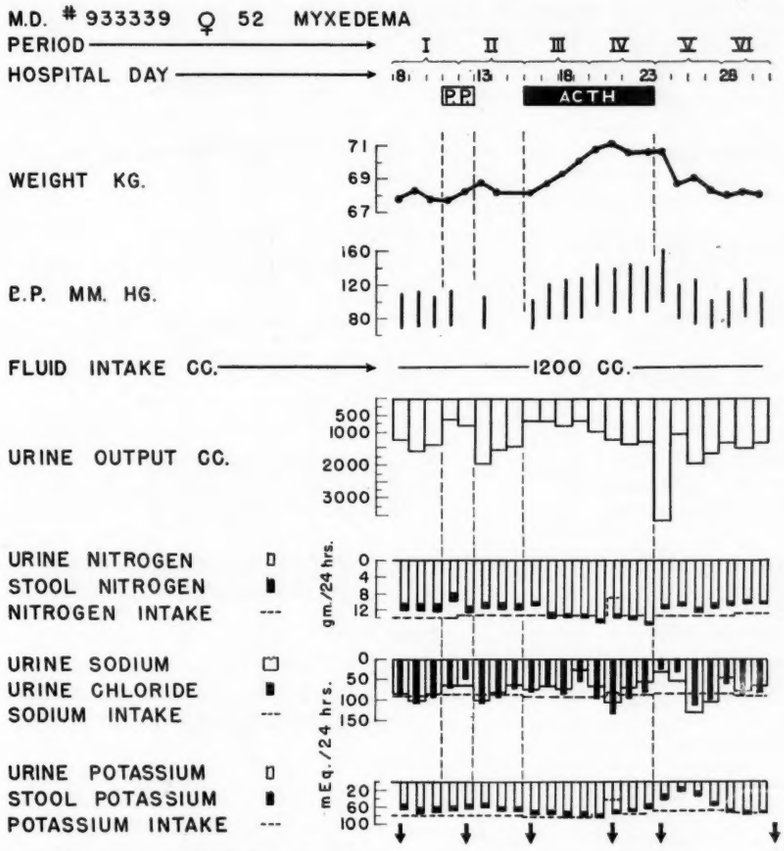
TABLE II

M. M. NO. 832794. A FIFTY-ONE YEAR OLD FEMALE WITH SIMMOND'S DISEASE*

Period	Hospital Day	Weight kg.	Fluid Balance (cc.)			Sodium Balance (mEq.)				Chloride Balance (mEq.)				Potassium Balance (mEq.)				Nitrogen Balance (gm.)				Urine Uric Acid mg.	Urine Creatinine gm.	Urine Creatine mg.	17-Ketosteroids Daily Average mg.
			Intake	Urine	Aver. Daily Balance per Period	Daily Intake	Urine	Stool (Aver.)	Aver. Daily Balance per Period	Intake	Urine	Stool (Aver.)	Aver. Daily Balance per Period	Daily Intake	Urine	Stool (Aver.)	Aver. Daily Balance per Period	Daily Intake	Urine	Stool (Aver.)	Aver. Daily Balance per Period				
I	12	59.00	1520	1120		95.2	91.4			102.5	97.2				62.2			12.4	10.8			357	1.14	202	0.67
	13	59.05	daily	1100			81.6				93.9				63.1			12.6	10.9			407	1.06	198	0.84
	14	59.00		1220		96.2	90.0			103.5	100.0				61.1			12.4	11.1			423	1.10	130	
	15	59.15		1080	+390	95.2	63.5	2.5	+11.3	102.5	78.8	1.0	+9.3	75.9	59.6	11.0	+3.4		10.8	0.9	+0.7	440	1.10	152	0.57
II	16	59.20	1520	1235		98.4	124.3			105.7	120.0				58.2				10.2			420	1.04	222	
	17	59.10	daily	1060		96.4	60.2				72.3				56.3			13.7	11.3			425	1.14	133	0.92
	18	59.34		1460			98.5			103.7	110.6				62.5				10.8			345	1.14	175	0.99
	19	59.19		1140	+295	99.4	95.4	1.5	+1.6	106.7	104.6	0.4	+2.7	78.8	50.2	6.0	+16 0	14.0	10.2	0.5	+2.6	257	1.23	103	
III ACTH† 33 mg.	20	59.22	1520	1210		99.0	86.9			103.0	103.9				67.6			12.9	11.6			436	1.05	218	
	21	59.31	1520	1000		102.0	59.0			106.0	85.2				61.8			13.2	10.6			256	1.20	120	1.21
	22	59.47	1520	1270		99.0	81.8			103.0	95.5				64.0				12.1			490	0.95	114	1.35
	23		1640	1375		101.0	102.7			105.0	104.0				55.0				10.7			480	1.07	165	
	24	59.55	1520	1460	+280	99.0	102.7	2.3	+11.5	103.0	111.2	0.6	+3.4	86.0	61.3	7.8	+16.3	12.9	11.6	0.8	+0.8	495	1.01	190	1.53
IV ACTH† 66 mg.	25	59.63	1520	1210			92.2				110.1				69.2				11.7			537	1.05	109	1.31
	26	59.62	daily	1660			63.4				85.4				50.8				11.9			456	1.05	50	
	27	59.39		1450			63.6				74.6				49.9				11.3			523	1.22	0	
	28			970			58.4				66.6				44.6				12.0			500	1.13	0	1.46
	29	59.70		1160	+230	100.0	100.4	3.5	+21.6	107.4	118.4	1.3	+15.3	74.8	60.8	9.9	+9.8	13.4	13.3	0.9	+0.5	522	1.04	209	2.56
V	30	59.40	1520	1060			82.4				106.2				38.0				11.8			408	0.96	270	2.21
	31	59.80	daily	1280			149.6				159.5				52.5				10.9			447	1.04	38	1.06
	32	58.44		1700			172.5				161.5				57.4				10.4			411	1.12	459	
	33	59.60		1340			94.8				100.2				76.6				10.6			320	1.21	523	
	34	59.70		1725			139.4				131.8				85.0				11.3			427	0.36	0	
	35	59.96		1460	+95	110.6	120.2	2.2	−18.1	118.1	109.2	0.7	−10.7	74.5	72.4	7.7	+3.2	12.6	11.0	0.7	+0.9	436	0.90	80	0.43
VI	36	59.15	1520	1420			86.3	2.2			93.7	0.7			74.2	7.7			11.1	0.7		426	0.89	85	
	37	59.24	daily	1420			103.2				109.1				75.0				11.1			453	0.99	0	
	38	59.00		1060			75.8				80.6				57.7				10.6			429	0.90	111	
	39	59.30		1130			65.3				80.0				64.2				10.9			429	1.05	134	
	40	59.50		1420			87.9				111.5				75.5				10.9			446	1.06	0	
	41	59.73		1280	+230		81.9	2.4			94.2	0.9			59.8	8.0			10.6	0.8		413	0.94	0	0.67
VII ACTH‡ 104 mg.	42	59.70	1520	1620		99.1	243.0			98.7	196.0			74.8	105.5			11 7	11.6			595	1.17	0	1.62
	43	59.36	daily	880	+270	94.6	96.8	4.2	−77.1	95.5	101.6	1.6	−54.9	71.9	46.6	11.4	−14.1	11.1	10.7	1.2	−1.0	444	1.06	0	0.88
		59.93																							

* = Daily Rx Thyroid 15 mg. DCA 2 mg.
† ACTH given in periods III and IV = Lot 37-K.E.
‡ ACTH given in period VII = Lot 37-KG

tract was given. (Fig. 2.) On one day of the initial study, the sixth day of ACTH administration, the patient was unable to complete her diet. In conjunction with ACTH administration a rise in blood pressure occurred. Following withdrawal of ACTH administration. It is of interest that she lost 3 kg. during the entire study, on a diet slightly greater than that on which her weight had remained constant when myxedematous. The only untoward events of this second study were that on two days the



SERUM CO_2 CONTENT mEq./L.		26.3	25.9	23.8	26.9	26.7
" CHLORIDES	"	98.0	98.0	91.5	86.2	101.4
" SODIUM	" 131.3	130.4	131.1	125.1	123.8	132.6
" POTASSIUM	" 4.5	5.2	4.6	4.7	4.8	5.4
" URIC ACID	mg./100 CC.	2.5	2.6	1.6	1.9	2.0
" UREA NITROGEN	"	23	25	17	15	21
" PROTEINS	gm./100 CC.	6.7	6.9	6.3	6.8	6.6
HEMATOCRIT % CELLS		31.8	32.5	30.1		31.8

P.P. = POSTERIOR PITUITARY, (E. R. SQUIBB & SON) 4 UNITS O.D.
ACTH = DAY 1 OF PERIOD III 66 MG., DAY 2 OF PERIOD III 70 MG.
REMAINDER OF PERIOD III & IV 75 MG. ARMOUR STAND. LOT G1112

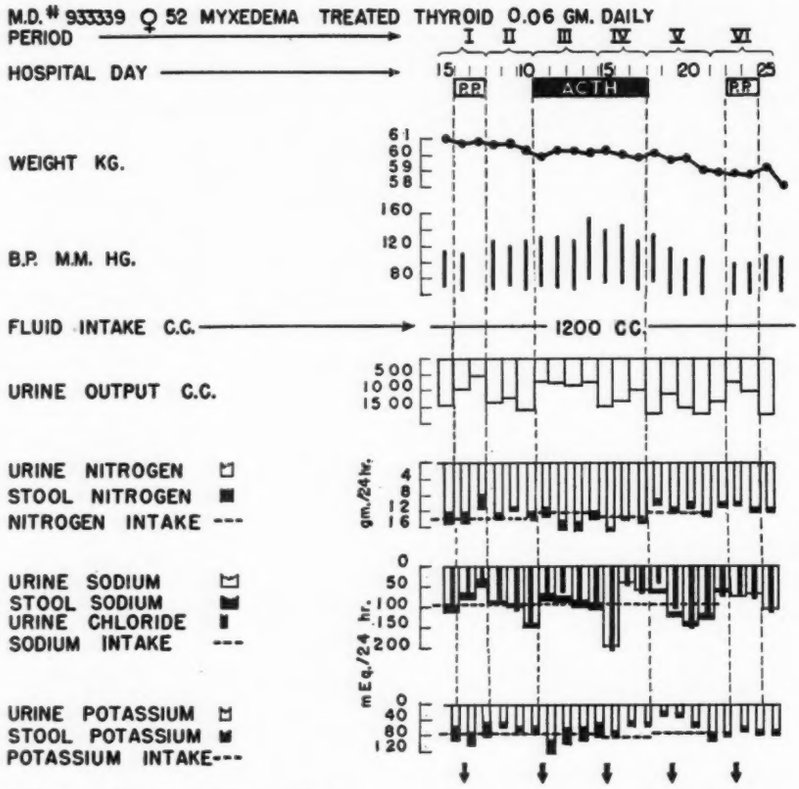
FIG. 2.

ACTH there was a prompt loss of weight and return in blood pressure to levels seen in the initial control periods.

In contrast, during the second study the patient remained asymptomatic except for a mild kerato-conjunctivitis. Her weight remained stationary during the period of patient had two or three loose bowel movements (day 3 of control period I, day 4 of ACTH period III). On the first such day there occurred loss of a portion of one urine specimen into a stool specimen. As a result of this and of the loose stools, the average daily stool nitrogen, sodium and potassium

of the two periods into which these two days fell, were significantly altered. (Fig. 3.) While receiving ACTH the patient's blood pressure again showed an upward trend, and again the pressure returned to lower levels when the hormone was discontinued.

pituitary did not lead to any change in weight. However, some reduction in urine volume and retention of sodium occurred. On day 3 of experiment 2, the second day of posterior pituitary administration, the sharply reduced sodium output is fallacious



SERUM CO_2 CONTENT	mEq./L.	27.0	26.1	25.5	26.7	25.0
" CHLORIDES	"	100.8	102.2	95.4	96.6	103.0
" SODIUM	"	135.0	135.2	129.2	131.6	135.4
" POTASSIUM	"	4.7	4.7	4.1	4.1	4.9
" URIC ACID	mg./100 cc.	5.5	4.8	3.2	2.8	4.9
" UREA NITROGEN	"	12	22	18	17	20
" PROTEINS	gm./100 cc.	6.9	5.9	6.5	6.2	5.7
HEMATOCRIT	% cells	46.5	39.4	40.8	43.3	38.7

P. P. = posterior pituitary (E.R. Squibb and son) 4 units O.D.
ACTH = 72 mg. Armour Standard Lot H2303 daily for 5 days
75 mg. Armour Standard Lot C 1112 daily for 6th and 7th day

FIG. 3.

Posterior Pituitary Extract Administration (Figs. 2 and 3, Tables III and IV). In the initial study the injection of 4 units of posterior pituitary extract daily resulted over two days in the gain of 1 kg., a sharp reduction in urinary output and in the retention of sodium and chloride. In the second experiment, done when the patient was euthyroid, similar dosages of posterior

due to the fact that it was on this day that the loss of one specimen of urine into a stool specimen occurred.

ACTH Administration—Electrolyte and Mineral Metabolism (Figs. 2 and 3, Tables III and IV). The administration of ACTH resulted in an initial retention of sodium and chloride. This was not maintained constantly throughout the period of hormone

TABLE III

M. D. NO. 933339. A FIFTY-TWO YEAR OLD FEMALE MYXEDEMA UNTREATED

Period	Hospital Day	Weight kg.	Fluid Balance (cc.)			Sodium Balance (mEq.)				Chloride (mEq.)		Potassium Balance (mEq.)				Nitrogen Balance (gm.)				Urine Uric Acid mg.	Urine Creatinine gm.	17-Ketosteroids Daily Average mg.	Corticoids Daily Average mg.
			Intake	Urine	Aver. Daily Balance per Period	Daily Intake	Urine	Stool (Aver.)	Aver. Daily Balance per Period	Daily Intake	Urine	Daily Intake	Urine	Stool (Aver.)	Aver. Daily Balance per Period	Daily Intake	Urine	Stool (Aver.)	Aver. Daily Balance per Period				
I P P *	8	67.8	1200 daily	1250			85.7				89.7		57.3				10.40			526	1.23	2.4	0.7
	9	68.25		1540			103.2				110.8		64.4				10.65			551	1.23		
	10	67.8		1410			89.6				97.2		62.4				10.68			439	1.18		
	11	67.75		650	−12	92.8	67.7	5.6	+0.6	100.0	69.8	80.1	58.4	12.4	+7.1	13.90	8.21	1.60	+2.32	478	.93	3.1	0.3
II P.P.*	12	68.26	1200 daily	800			65.0				59.4		59.6				11.30			682	1.21		
	13	68.78		1980			104.1				108.2		55.4				10.30			543	1.18		
	14	68.17		1560			81.4				96.8		63.6				10.53			479	1.15		
	15			1460	−250	91.6	66.6	2.8	+9.5	101.3	78.9	78.7	63.1	6.2	+12.1	13.47	10.62	1.18	+1.60	578	1.20	3.9	0.5
III ACTH†	16	68.13	1200 daily	700		93.2	74.7				82.8		71.9				10.01			750	1.20	5.1	0.6
	17	68.76		730		93.6	70.0				71.6		71.6				12.56			812	1.20		
	18	69.34		800		94.1	75.5				91.8		74.2				12.76			731	1.22		
	19	70.14		700	+468	94.1	30.0	2.2	+29.0	98.1	55.5	82.8	76.4	8.4	+0.9	13.85	12.94	0.87	+0.91	695	1.17	5.2	0.9
IV ACTH	20	70.89	1200 daily	1040		94.1	68.2	2.2		98.1	100.2	82.8	76.6	8.4		13.85	14.27	0.87		724	1.18	11.9	1.3
	21	71.06		1240		85.3‡	111.5			89.6‡	139.8	46.9‡	72.4	6.3		8.71‡	13.20			667	1.16		
	22	70.60		1370		93.2	75.7			98.6	101.4		67.5			13.57	13.50			641	1.20		1.3
	23	70.52		1300	−38	93.2	60.0	2.0	+10.6		82.1	79.3	59.3		−3.7		14.65	0.58	−2.13	702	1.21		
V	24	70.68	1200 daily	3440			36.5				29.8		37.5				10.92			431	1.01	7.6	1.4
	25	68.66		1080			54.4				39.5		15.1				10.35			513	1.04		
	26	69.01		1940			137.0				115.0		27.9				11.77			692	1.10		
	27	68.43		1680	−835	88.6	110.9	4.3	−0.4	95.3	106.9	70.9	53.8	7.4	+29.9	13.60	10.58	0.82	+1.88	654	1.12	7.1	1.2
VI	28	68.11	1200 daily	1340		88.6	51.4			95.3	63.4	70.9	71.0			13.60	10.16			652	1.10	7.3	0.6
	29	68.25		1520		95.9	82.8			101.0	92.6	78.7	75.4	4.0	+0.9	13.00	9.92			635	1.13		
	30	68.13		1435	−232		72.9	2.8	+21.6		83.4		72.6				10.15	0.45	+2.67	637	1.15		
																				Ten days later		5.5	1.1

* P.P. = Posterior pituitary (E. R. Squibb & Son) 4 units daily.

† ACTH = Day 1 of period 3–66 mg.; day 2, 70 mg. Day 18–23, 75 mg. Armour Standard—Lot H-2303.

‡ Patient refused supper; rejected food, analysed and subtracted from daily intake.

TABLE IV

M. D. NO. 933339. A FIFTY-TWO YEAR OLD FEMALE MYXEDEMA TREATED*

Period	Hospital Day	Weight kg.	Fluid Balance (cc.)			Sodium Balance (mEq.)				Chloride (mEq.)		Potassium Balance (mEq.)				Nitrogen Balance (gm.)				Urine Uric Acid mg.	Urine Creatinine gm.	17-Ketosteroids Daily Average mg.	Corticoids Daily Average mg.
			Intake	Urine	Aver. Daily Balance per Period	Daily Intake	Urine	Stool (Aver.)	Aver. Daily Balance per Period	Daily Intake	Urine	Daily Intake	Urine	Stool (Aver.)	Aver. Daily Balance per Period	Daily Intake	Urine	Stool (Aver.)	Aver. Daily Balance per Period				
I P.P.†	5	61.04	1200	1460			97.8				97.8		56.1				12.00			624	.80		
	6†	60.72	daily	934			66.5				73.0		68.8				12.23			767	.90		1.2
P.P.†	7†	60.87		521	+228	94.9	28.2	17.7	+13.0	96.3	32.8	70.7	45.2	28.9	−14.9	13.5	7.93	2.99	−0.21	482	.52		
	8	60.62	1200	1360			81.6				80.6		46.4				12.69			586	.87		
II	9	60.69	daily	1208			91.8				104.4		57.0				10.90			581	.92	4.0	1.5
	10	60.44		1600	−189	94.9	139.5	5.2	−14.6	96.3	139.6	70.7	56.3	8.4	+9.1	13.5	12.20	0.73	+0.84	619	.89		
	11	59.93	1200	740			65.1				69.4		85.6				11.25			793	.81	4.3	1.4
III ACTH**	12§	60.35	daily	740			68.1				60.6		60.0				14.40			605	.86		
	13§	60.31		800			82.8				88.0		55.0				14.60			770	.88	6.2	2.2
	14	60.18		760	+440	95.2	86.8	14.3	+5.2	97.5	98.4	69.0	46.7	32.0	−24.8	11.9	11.65	2.05	−3.13	629	.71		
	15	60.35	1200	1477		97.8	192.4			101.6	204.0		66.2				16.10			900	.92		
IV ACTH††	16	60.03	daily	1350		98.5	34.8			102.3	42.7		42.4				13.50			647	.82	10.5	3.8
	17	59.80		960	−62		51.8	1.0	+4.3		58.8	74.8	45.5	5.5	+17.9	13.4	14.20	0.43	−1.63	763	.82		
	18	60.09	1200	1700			52.7				33.2		17.7				9.20			962	.76	10.3	1.8
	19	59.62	daily	1100			109.0				96.4		21.4				11.00			621	.84		
V	20	59.84		1520			132.6				142.5		45.0				9.90			627	.78	6.4	1.6
	21	59.10		1680	−300	94.5	116.6	4.2	−12.4	99.0	128.0	67.5	76.9	8.4	+19.0	11.8	12.00	0.92	+0.36	786	.97		
	22	58.90	1200	1300			58.0				66.8		68.1				9.80			626	.89		
VI P.P.†	23†	58.92	daily	690			64.8				65.0		54.8				9.60			654	.83	5.4	0.9
P.P.†	24†	58.84		1000			60.8				70.9		64.3				11.30			611	.86		
	25	59.34		1680	+33		97.4	1.7			107.5		62.4	8.7			11.30	0.72		568	.89		
	26	58.00																					

Explanations:
* = R_x thyroid 60 mg. daily.
† P.P. = Posterior pituitary (E. R. Squibb) 4 units daily.
‡ = ? Amount of urine included in loose stool. Two loose stools this day.
§ = Seven stool specimens, loose, in these two days.
** ACTH = 72 mg. daily Armour Standard Lot H-2303 for first 5 days.
†† ACTH = 75 mg. daily Armour Standard Lot G-1112 for last 2 days.

administration. Beginning on the second or third day after ACTH withdrawal a diuresis of sodium and chloride occurred. When euthyroid, these effects of ACTH were less striking. In conjunction with the administration of ACTH a striking fall in the serum sodium and chloride values occurred. This appeared to be of equal magnitude in both studies.

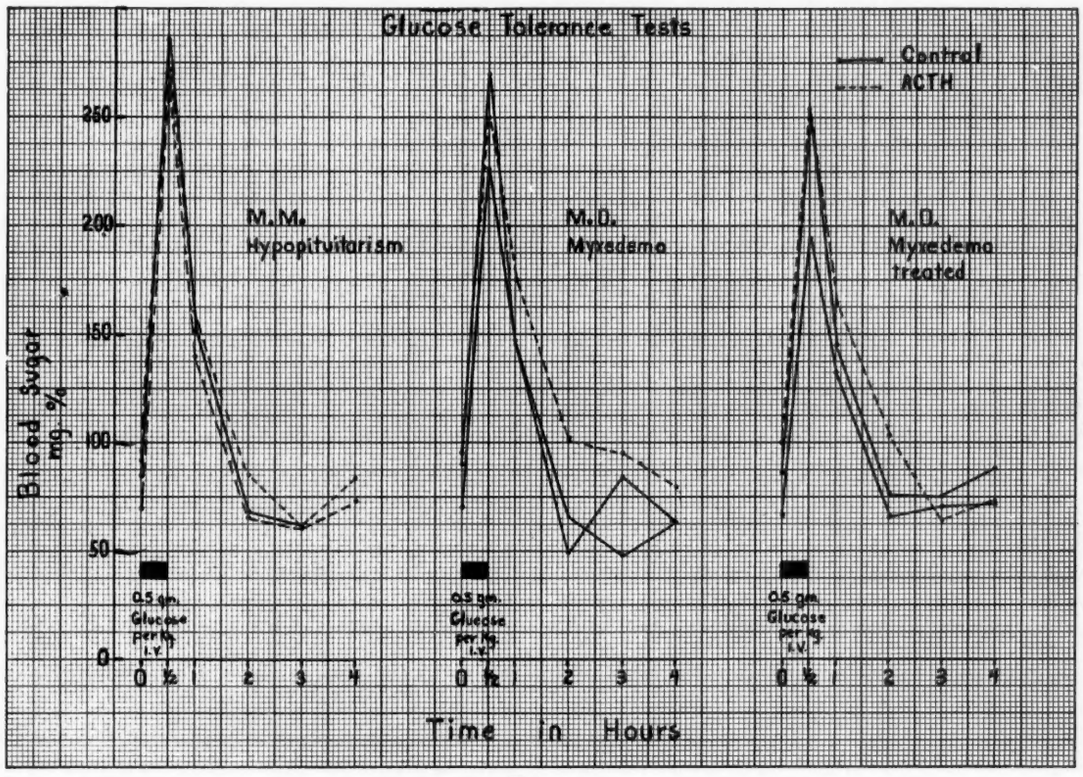


FIG. 4.

While myxedematous, ACTH administration was accompanied by an increased excretion of potassium. This was even more striking in the second study done while the patient was receiving thyroid. In neither study was the serum potassium level altered. After withdrawal of the hormone a striking retention of potassium was observed in both experiments. No increase in serum bicarbonate content was observed in either experiment during ACTH administration.

Measurements of calcium and phosphorus balance were not made in this patient.

Protein Metabolism (Tables III and IV, Figs. 2 and 3). During the ACTH periods an increased excretion of nitrogen occurred resulting in a negative nitrogen balance. This was more evident in the study made when the patient was euthyroid. The serum urea nitrogen level showed inconsistent fluctuations during ACTH administration. In both studies a significant fall in serum uric acid levels occurred, and in both there was an increase in uric acid excretion in the urine. Creatinine excretion remained constant with the exception of day 3 of control period I in the second study, on which day loss of one specimen of urine occurred.

17-Ketosteroid Excretion and "Corticoid" Excretion (Tables III and IV). The administration of ACTH resulted in an increase of 100 to 200 per cent in the urinary excretion of 17-ketosteroids. This occurred in both studies. ACTH also led to an increase in "corticoid" excretion in the urine, and after the hormone was discontinued this returned over a period of days to control levels. During the control periods the patient, when myxedematous, excreted less

than the normal amounts of "corticoids." Following thyroid replacement therapy the excretion of the "corticoids" increased to within the normal ranges (see initial control period of study 2, Table IV).

Carbohydrate Metabolism. Fasting blood sugar levels were not altered significantly during the periods of ACTH administration. During these periods the increase in reducing substances present in the twenty-four-hour urine, as determined by Benedict's quantitative method, was of questionable significance (from 1 gm. to a peak of 3.6 gm. when myxedematous and from less than 1 gm. to 1.5 gm. when the patient was receiving thyroid). Glucose tolerance tests were done before, during and after ACTH administration. (Fig. 4.) The peak of the curve was not increased during the hormone injections; however, the values at the end of two hours were greater than the corresponding control values. This has been observed in both studies.

TABLE V

M. M.—Simmonds' Disease					M. D.—Myxedema					M. D.—Myxedema Treated			
Period	Days	ACTH (mg. per day)	BMR (%)	Serum Cholesterol (mg. %)	Days	ACTH (mg. per day)	BMR (%)	Serum Cholesterol (mg. %)	I^{131} Uptake (%)	Days	ACTH (mg. per day)	BMR (%)	Serum Cholesterol (mg. %)
I	4	0	−40	...	4	0	−22	338	2	3	0	− 1	257
II	4	0	−31	258	4	0	−21	348	..	3	0	−13	220
III	5	33	−22	209	4	66–75	−17	300	..	4	72	− 8	220
IV	5	66	−16	231	4	75	−20	325	0	3	72–75	− 9	...
V	6	0	....	...	4	0	....	304	..	4	0	....	215
VI	6	0	−33	321	3	0	−23	...	..	4	0	−17	210

Basal Metabolism (Table V). The basal metabolism in the initial study on this patient remained constant throughout and there was no significant trend in the serum cholesterol values. The twenty-four-hour up-take of radioactive iodine was not increased by the administration of ACTH as determined after eight days of treatment. In the later study, made while the patient was receiving thyroid medication, the basal metabolism fluctuated considerably. There was, however, no significant change in serum cholesterol.

Eosinophile Counts (Table VI). In the first study the patient responded to the initial injection of ACTH with a less than normal fall in the per cent of circulating eosinophiles. However, counts done on the fourth to eighth day of hormone injections revealed that after continued ACTH the circulating eosinophiles disappeared. In the second study when the patient had

TABLE VI
EOSINOPHILE COUNTS

Patient M. D.	Period	Fasting Eosinophile Count per $mm.^3$	Fall in Eosinophile Count in 4 Hours after Initial Injection of ACTH %
Study I—Myxedema:	I Control Day 4	125	
	III ACTH Day 1	125	−35
	IV ACTH Day 5	0	
	ACTH Day 6	0	
	ACTH Day 7	0	
	ACTH Day 8	0	
	V Control Day 2	130	
Study II—Myxedema treated:	III ACTH Day 1	125	−52

received three months of thyroid therapy, the response to the initial injection of ACTH was normal.

COMMENTS

In the patient with *long-standing hypopituitarism* the effects of ACTH were, on the whole, minimal in character. There was evidence of sodium and chloride retention, and after hormone therapy was stopped there was a diuresis of these ions. There was an increase in the excretion of 17-ketosteroids in the urine although the magnitude of the rise was not impressive. Finally, there was a moderate increase in uric acid excretion. However, there was no demonstrable alteration in carbohydrate or nitrogen metabolism, nor in calcium or phosphorus metabolism.

It is possible to explain the over-all minimal response of this patient to ACTH on the ground that many years of adrenal atrophy from lack of endogenous pituitary stimulation had permanently altered the ability of the gland to respond to exogenous hormone. In addition, it appears reasonable to postulate that the atrophy did not involve all functions of the gland to an equal extent in order to explain the observed response to ACTH in the sphere of sodium metabolism and 17-ketosteroid excretion when no response occurred in carbohydrate or nitrogen metabolism. It may be that these are the most sensitive indices of adrenal cortical stimulation. It is of interest that Greep and Deane[40] have claimed that those portions of the adrenal which are associated with carbohydrate and nitrogen effects show more atrophy following hypophysectomy than those which they believe influence sodium metabolism in the rat.

The reaction of this patient to the highest dosage of ACTH (104 mg.) remains unexplained. There is a possibility that posterior pituitary hormones, which were present in considerable amounts in this preparation, played a role in the cramps and nausea that ensued.

The increase in basal metabolism which occurred during ACTH administration deserves comment. The preparation of ACTH employed contained negligible amounts of thyrotropic hormone, as assayed in the Armour Laboratories, hence the rise in basal metabolic rate cannot be ascribed to thyrotropic hormone contained in the ACTH. It is possible that the increase in basal metabolism reflects an increase in functional activity of the tissues in response to ACTH. In view of the minimal evidences of such activity, however, this seems unlikely. It is tempting to speculate that the increased activity of adrenal glands in this patient had a directly stimulating effect upon the thyroid.

In the *patient with myxedema*, however, no indications of increased thyroid activity could be demonstrated during the administration of ACTH. No rise in basal metabolism or up-take of radioactive iodine occurred during the ACTH study done when the patient was myxedematous. In addition, in this patient an attempt was made to determine to what extent myxedema modifies the ability of the organism to respond to ACTH. It seems evident that in the presence of profound hypothyroidism the response to ACTH was similar to the response some three months later when the patient was no longer myxedematous. A negative nitrogen balance, increased uric acid, "corticoid" and 17-ketosteroid excretion occurred in both studies. The most striking difference between the two studies is that much more marked fluid retention and greater changes in sodium and chloride metabolism took place in the initial ACTH study when she was hypothyroid than in the second experiment, after she had received sufficient thyroid medication to relieve her myxedema. To explain this on the grounds that there was greater stimulation of adrenal activity in the hypothyroid state seems implausible since other evidences of increased adrenal activity were as great when the patient was euthyroid, i.e., increased nitrogen, 17-ketosteroid and "corticoid" excretion. Four other possibilities must be considered. Eppinger[41] has reported that in hypothyroid states the ability to

excrete a given load of saline is much retarded. In view of this the hypothyroid individual might well show a greater than normal response to a hormone inducing sodium retention. A second possibility is that, when hypothyroid, the patient was in borderline cardiac failure (cardiac enlargement, peripheral edema and minimal elevation of venous pressure were present) and that under these circumstances ACTH which favored sodium retention evoked an abnormally marked response. This idea is supported by the fact that her heart by the time the second study was undertaken had decreased 2.4 cm. in its transverse diameter and peripheral edema was no longer present, and in this instance the retention with ACTH was far less marked. Thirdly, how much of this sodium and fluid retention can be ascribed to the ACTH itself and how much may be dependent upon the posterior pituitary hormones present in the preparation is difficult to state. Examination of Figure 2 shows that the weight gain, fluid and sodium retention during the two days the patient received posterior pituitary extract are quite similar to those occurring in the first two days of ACTH. In the second experiment (Fig. 3) some reduction in urine output and sodium and chloride excretion occurred again although in this experiment posterior pituitary extract led to no gain in weight. In other words, when hypothyroid the patient appeared more than usually sensitive to posterior pituitary. Fourthly, it is probable that less fluid and sodium retention occurred during the second study than was expected due to the episode of diarrhea which ensued on the fourth day of ACTH administration. Analyses of stool volumes were not made but a considerable loss of electrolytes and nitrogen was evident. (Fig. 3, Table IV.)

It is of interest that prior to thyroid therapy this patient, without known adrenal disease, had a less than normal fall in circulating eosinophiles following the initial ACTH injection. This may be related to a delay in absorption from the site of injection. Subsequently, with continued ACTH injections, the eosinophiles disappeared entirely. Following replacement therapy with thyroid the extent of fall in circulating eosinophiles following the first dose of ACTH was normal.

SUMMARY

The metabolic changes observed in a patient with *long-standing hypopituitarism* and presumed atrophy of the adrenal glands during ten days of ACTH administration were minimal. Retention of sodium and chloride, some increase in 17-ketosteroid excretions, in uric acid excretion and an unexplained rise in basal metabolism were noted. No alteration in carbohydrate or nitrogen metabolism was observed.

The metabolic changes observed in a patient with *primary myxedema* during eight days of ACTH administration were comparable to those observed in the same patient during a second period of seven days of ACTH administration after euthyroidism had been achieved. Hence the presence of a normal thyroid function is not essential to the function of ACTH. Increased potassium excretion, a negative nitrogen balance, increased uric acid excretion, and increased 17-ketosteroid and "corticoid" excretion were observed in both studies. A greater weight gain and retention of sodium and chloride were observed in the study made before thyroid treatment was instituted. In both, changes in carbohydrate metabolism were equivocal. While myxedematous the initial injection of ACTH was accompanied by a less than normal fall in circulating eosinophiles, although these cells subsequently disappeared from the blood with continued hormone administration. ACTH resulted in no significant alteration in thyroid function in either study.

Mild but consistent hypertension appeared in both studies during ACTH administration.

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Prepared Insulin Mixtures in the Treatment of the Severe Diabetic Patient

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TREATMENT of the diabetic patient requiring more than 40 units of insulin daily has been a challenge to the ingenuity of the physician because the existing types of insulin have failed to provide completely adequate replacement therapy. It is commonly accepted that about one-half of all diabetic patients can be managed by diet alone and without insulin. Twenty-five per cent need less than 40 units of insulin daily and offer no therapeutic problem since any type of insulin-diet regimen will satisfy their requirements. This group can obtain good diabetic control with regular, protamine zinc or globin insulin.

The so-called "severe" diabetic patients comprise about 25 per cent of the remaining diabetic population. They were benefited tremendously by the introduction of longer-acting insulin which reduced the number of their injections each day. However, marked postprandial glycosuria plus nocturnal hypoglycemia so characteristic of slow-acting insulin presented a problem, especially to those taking large doses, and led first to the practice of administering separate injections of rapidly acting regular insulin and then to mixing both regular and protamine zinc insulin.

Extemporaneous mixtures received their initial impetus in 1941 through the work of Ulrich[1] although limited studies had been reported previously. Within a year after his observations the studies of Peck,[2] Colwell[3] and MacBryde[4] established the validity of such mixtures. As the use of mixtures gained wider acceptance attempts were made to evolve an ideal mixture which could satisfy the insulin requirements of all diabetic patients in a single daily injection. Adequate management of severe diabetes mellitus would seem to be the definitive test for the critical evaluation of such insulin modifications. The clinical experience with prepared insulin mixtures in such a group of patients during the past four years is the subject of this paper.

SELECTION OF MATERIAL

Insulin, unlike other therapeutic agents, becomes an integral part of a patient's mode of living; it is only infrequently administered under the controlled conditions of hospital supervision. Its actual performance therefore can be measured only under the varying circumstances of normal living. For this reason, 185 patients were selected from private practice, embracing a wide range in age and physical condition. Their daily insulin requirement was from 40 to 160 units, averaging 72.2 units. The patients were ambulatory, engaged in every sort of occupation, subject to a variety of different physical demands and activities. Fifty-six of these were under 18 years of age and formed a special subgroup for this study in view of the recognized severity and instability of diabetes in the juvenile patient.

The diets contained an average of 200 to 250 gm. of carbohydrate, with a minimum of 150 gm. for obese patients. About one-quarter of the patients partook of even higher carbohydrate intake up to 300 and 350 gm.

Criteria for evaluation of insulin efficiency included symptomatic as well as chemical control, where possible, without provoking severe hypoglycemia. Thus, besides freedom

from thirst, polyuria, weight loss and ketonuria, attempts were made to maintain blood sugar levels at postabsorptive periods during the day at normal values or at least within the threshhold level. If the latter could not be achieved without hypoglycemia, higher postabsorptive blood sugar levels were accepted. Glycosuria was treated in like manner with emphasis on minimal daily excretion whenever feasible. Such optimal control was possible in only one-half the patients. Symptomatic control, a recognized compromise for the severe, "brittle" diabetic patient, was used for the other half. According to Allan[5] it is in this group, "10 to 16 per cent of all cases . . . that limited control which would not be approved in other cases must be considered acceptable."

ANALYSIS OF CLINICAL MATERIAL

NP42 and NP50. In 1944 a number of severe diabetic patients using extemporaneous mixtures were placed on a modified protamine zinc insulin, NP42, a buffered neutral equivalent of a 2:1 mixture of regular and protamine zinc insulin. It was soon apparent[6] that the majority of these patients suffered unusually frequent hypoglycemic episodes before noon and a number noted inadequate lapover during the night resulting in nocturia and morning hyperglycemia. The insulin found better acceptance with the juvenile diabetic patients whose late breakfast and early lunch prevented noon hypoglycemia and whose early dinner and bedtime coincided more precisely with the rapidly waning nocturnal effect of NP42. Adults, however, with a late dinner hour and the habit of a bedtime snack required more prolonged insulin effect during their sleeping hours.

In 1945 a slight alteration in the modification by an increase of its protamine content from 0.42 mg. to 0.50 mg. resulted in the preparation NP50. This proved of some benefit in reducing the impact of noon hypoglycemia and provided more lapover during sleeping hours. In the next three years seventy-four patients tried NP50 (Table I) but only 20 patients obtained sustained and satisfactory insulin coverage. Two-thirds of the patients continued to note pre-lunch hypoglycemia and nocturia. These fifty-four patients found their problems solved by the use of mixtures in oversized vials containing slightly more protamine zinc insulin than had obtained in the 2:1 ratio of NP50.

TABLE I
EXPERIENCE WITH NP42 AND NP50

20 patients obtained satisfactory insulin coverage for over three years
Average daily insulin dose—72.2 units
54 patients found the insulin inadequate due to:
(1) too rapid forenoon effect—11 A.M. hypoglycemia
(2) inadequate lapover resulting in nocturia
These responded to mixtures containing more PZI e.g., 10:5, 10:6 and 10:7 in oversized vials

NPH50. By the summer of 1948 a crystalline NP50 was made available as NPH50. This modification offered the advantages of stability and slightly longer activity. This was substantiated clinically by the observation that not only could the twenty patients originally carried on NP50 change over to the new crystalline modification, but many former failures with NP50 found NPH50 satisfactory. The latter now noted adequate lapover abolishing the formerly disturbing nocturia. The further slowing of the rapid insulin effect afforded freedom from annoying hypoglycemic episodes before lunch. Patients using extemporaneous mixtures or oversized vials in 2:1 ratio could be transferred to this modification with equal success. In all, seventy-two patients requiring an average daily dose of 66.6 units of insulin have obtained adequate insulin coverage for the past ten months. (Table II.)

TABLE II
EXPERIENCE WITH NPH50

72 patients obtained optimum insulin coverage for 10 months (16 juvenile and 56 adults)
Average daily insulin dose—66.6 units
8 juvenile patients found NPH50 inadequate due to:
(1) nocturia in 4 requiring 10:7 and 10:8
(2) prenoon polyuria and late afternoon hypoglycemia in 4
4 adults suffered 11 A.M. hypoglycemia corrected by oversized vials with more PZI

Fifty-six adults with severe diabetes displayed good results in contrast with the experience in this group on NP42 and NP50. Only four failed to do well, and in every instance because of unusually prolonged fast between breakfast and lunch. This is characteristic of commuters who have breakfast at 6 or 7 A.M. and have to wait until 1 o'clock for lunch. The remaining fifty-two have managed quite well with good night lapover and without nocturia or noon hypoglycemia, even in 120 unit doses.

NPH50 failed in eight of the twenty-four juvenile diabetic patients. Four children complained of the same difficulty with nocturia as the adults, and were satisfied with oversized vial mixtures containing less regular insulin activity. Only four patients reported a lack of sufficiently rapid forenoon effect from the 2:1 ratio in NPH50 and required approximately a 3:1 ratio in an oversized vial. Recently these four patients found that the addition of 1 or 2 cc. of regular insulin to NPH50 provided the necessary postbreakfast momentum which prevented forenoon glycosuria. Apparently NPH50 is a preparation in which any added regular insulin is recoverable. This point makes NPH50 especially practicable for those physicians employing ratios of 3:1.

Oversized Vials. The availability of an oversized 20 cc. vial containing 10 cc. of regular insulin (U 80) which permitted the addition of any desired amount of protamine zinc insulin provided several advantages over extemporaneous mixtures. Apart from the obvious one of convenience, it insured uniformity of admixture superior to that obtained by the patient's twirling an air bubble in the syringe. Furthermore, accuracy of measurement of the daily dose of insulin is better secured by the use of a single vial. However, the need for accuracy of measurement and sterile precautions in introducing the protamine zinc insulin into the vial is a disadvantage. Maintenance of sterility demands a technic not ordinarily expected from patients, and the prospect of contamination looms as a possible hazard if preparation of the mixture is entrusted to the patient. Because of the need for precise attention in the addition of protamine zinc insulin, the mixtures used in this study have all been prepared by one trained individual.

Experience of the past four years with mixtures in oversized vials is shown in Table III. The ratio of each mixture is marked in units of 10 inasmuch as all vials contain a basic 10 cc. of regular insulin. The consequent or second figure in the ratio refers to the amount of protamine zinc insulin, e.g., 10:7 means 10 units or cc. of regular insulin to 7 units or cc. of protamine zinc insulin.

TABLE III

RESULTS WITH MIXTURES IN OVERSIZED VIALS

Ratio of R:PZI in Mixture	No. of Good Results	No. of Poor Results	Reason for Failure	Final Mixture
10:5	28	13	Nocturia and noon hypoglycemia	10:6 10:7 10:8
10:6	17	28	Nocturia and noon hypoglycemia in 18	10:7 10:8
			5 A.M. hypoglycemia in 7	10:5
			11 A.M. polyuria in 3	10:5
10:7	43	12	Nocturia in 2	10:8
			5 A.M. hypoglycemia in 6	10:5 10:6
			5 P.M. hypoglycemia in 4	10:5 10:6
10:8	18	0		

The twenty-eight patients carried successfully on a 10:5 mixture were transferred originally from NP42 because of its already described limitations. The thirteen failures with this ratio presented the difficulties characteristic of inadequate protamine effect. A change to 10:6, 10:7 or 10:8 obviated those symptoms.

The failures outnumbered successes with the 10:6 ratio. This mixture seemed to be more variable than the others, with symptoms fluctuating between too little and too much protamine effect.

The most useful ratio appeared to be 10:7. The forty-three patients using this mixture represented many who found

NP42 and NP50 ineffectual and required something intermediate in action between those 2:1 preparations and protamine zinc insulin alone. This ratio permitted many business people to pursue their regular work program with irregular meal schedules

TABLE IV

DISTRIBUTION OF MIXTURES USED FOR THE ENTIRE GROUP OF PATIENTS

Mixture	Total No. of Patients		No. of Juvenile Patients	
NPH50	72	54.2%	16	45.5%
10:5	28		4	
10:6	17	42.1%	5	45.5%
10:7	43		9	
10:8	18		6	
10:10	3			
10:4	2		2	
10:3	2		2	
Total	185		44	

without noon hypoglycemia. Indicative of the excellent lapover is the fact that only two patients had nocturia. In fact, the somewhat prolonged nocturnal effect of this ratio caused late afternoon and early morning hypoglycemic reactions in ten patients.

The 10:8 ratio represents the refuge of eighteen patients whose requirements and living habits were such that any mixture with less prolonged effect resulted in nocturia. These patients had progressed from NP42 through all the ratios, working up to one with maximum protamine effect. An unusual need for prolonged effect was exhibited by three patients whose control could be satisfied only by a 10:10 ratio. (Table IV.) This is comparable to the same incidence of this ratio in Sprague's[7] recent experience. It is noteworthy that ratios 10:3 and 10:4 were required only for the very young children.

COMMENT

The need for insulin better suited to the diabetic patient's requirements is indicated by the increasing number of reports on modifications. The patients with severe diabetes, varying physical demands and diverse dietary habits, living in a constantly fluctuating environment are the ultimate and crucial test for any insulin modification. Without altering the routine of such patients an attempt was made to find the modification adapted to each individual's requirements. Obviously, no single insulin preparation was applicable to the entire group. By an "educated guess" the proper ratio was arrived at for the majority of patients, suitable to the particular program of each. The minority required a series of trials with different preparations until the ideal one was found. When the appropriate mixture was determined, all patients were followed through the natural variations of insulin dose associated with infections, acute emotional tensions, periods of increased physical activity, etc. It was possible to meet these divergent situations with altered insulin dosage of the selected mixtures.

Several investigators advocate the adoption of a 2:1 or 3:1 ratio in a mixture for all diabetic patients. As seen in Table IV, about one-half the patients required some form of a 2:1 ratio (either in an oversized vial or as NPH50). With few exceptions, the remaining half needed a ratio closer to 3:2 originally advocated by Ulrich.[1]

The experience of Adlersberg and myself[8] with extemporaneous mixtures led us to conclude that "although the use of a single mixture would simplify the treatment of diabetes, there is at present no agreement as to the ideal ratio." This statement holds true today.

NPH50 proved successful in almost 40 per cent of the patients with severe diabetes. The success of this preparation in answering the challenge of such a group coupled with the excellent results obtained in a series of patients with milder diabetes (not included in this report) warrants the conclusion that NPH50 deserves further consideration for general availability. Its stability, predictability and flexibility (though limited) justify its trial in all diabetic patients. Where it fails, as it did in over one-half the remaining patients with severe diabetes, a "tailor-

made" insulin is required. For such highly individual preparations the oversized vial offers a distinct convenience in addition to other advantages already described. However, its availability for general use is unlikely at present in view of the possibility of contamination and the question of legal responsibility for the final mixture.

SUMMARY

1. Severe diabetes mellitus in 72 of 185 patients could be satisfactorily controlled by a prepared insulin mixture, NPH50.

2. The remainder required mixtures of varying proportions which were most conveniently and uniformly prepared in oversized vials.

3. The availability of NPH50 generally may be desirable since it provided adequate insulin coverage for 40 per cent of the patients with severe diabetes mellitus and was also applicable to patients with low to moderate insulin requirements.

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Diabetes Mellitus and Liver Dysfunction*

Etiologic and Therapeutic Considerations

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MOST authorities in the field of diabetes believe that hepatic abnormalities in diabetes are either incidental or secondary to poor diabetic control[1] while others believe that hepatic disease may cause the diabetic syndrome (hyperglycemia with glycosuria) in many patients.[2] Those attaching no etiologic significance to hepatic dysfunction in diabetes have emphasized the necessity for diet restriction and frequently for insulin in the treatment of the disease, while proponents of the thesis that hepatic disorders may be responsible for disturbances in the regulation of carbohydrate metabolism stress the need for intensive hepatic therapy, the employment of insulin being considered secondary and, at times, unnecessary.

Numerous studies have been made of the relationship of liver disease to diabetes. It has been shown that the integrity of the liver may have an important role in determining the character of the glucose tolerance curve.[3] Clinical evaluations have frequently revealed hepatomegaly as a complication in poorly controlled juvenile diabetes[1a] as well as in 30.4 per cent of patients with diabetic neuropathy.[4] Liver function studies in diabetes have shown hepatic dysfunction to be present in 28.0 to 36.8 per cent of patients.[1b,5,6] Fatty livers have been found upon pathologic evaluation of diabetic patients whose disease was associated with complications[7] and cirrhosis of the liver has been reported in from 0.5 per cent to as high as 12.7 per cent of diabetic patients.[1c,d] Prolonged fatty infiltration of the liver in the diabetic has been shown to lead to hepatic cirrhosis.[1e,8]

MATERIAL AND METHODS

Hepatic studies were performed on 380 diabetic patients in an effort to determine the etiologic and therapeutic significance of hepatic dysfunction in diabetes. Joslin's criteria[1c] for the diagnosis of diabetes were employed. Blood sugars were determined by the method of Folin and Wu on venous blood and standard (one dose) oral glucose tolerance tests were performed when necessary. Patients with hemochromatosis and obvious intercurrent affections of the liver such as metastatic malignancy, infectious hepatitis and biliary obstruction were excluded from these clinical studies.

There were 126 male and 254 female patients. One hundred thirty patients were studied on an outpatient basis and 250 were studied as hospital patients. Two hundred twelve had medical abnormalities including twenty-two with diabetic coma, thirty with vascular diseases as the major pathologic condition and fourteen with active tuberculosis. Thirty-four had primary surgical diseases, twenty-four of whom had gangrene requiring operative intervention. Six had urologic diseases, six were admitted for fractures, six were receiving therapy for ear, nose and throat or eye diseases, five were being treated for gynecologic disorders and one was receiving therapy for a tooth abscess. Total insulin requirements before study varied from none on a diabetic diet to 132 units daily, with an over-all average of 17 units. Duration of diagnosed diabetes ranged from discovery at the time of hospitalization to twenty-seven years, with an average duration of six years.

The liver function tests employed were the serum bilirubin, bromsulfalein excretion, total serum cholesterol and esters, serum albumin and globulin and the cephalin-cholesterol flocculation. Standard oral and intravenous glucose tolerance tests, serum alkaline phosphatase, urine bile and urobilinogen, thymol

* From the Diabetic Service, Department of Internal Medicine, Jersey City Medical Center, Jersey City, N. J.

turbidity and prothrombin time were included in the liver function battery of tests in some instances.

Cephalin-cholesterol flocculation tests with 2 to 4 plus reactions at forty-eight hours were considered abnormal. Total serum proteins less than 6.5 gm. per 100 cc., reversal of the albumin-globulin ratio, and serum bilirubin levels above 1.0 mg. per 100 cc. were considered abnormal. Normal total cholesterol standards ranged between 150 to 230 mg. per 100 cc. with 50 to 70 per cent of the total being esterified. Retention of 5.0 per cent or more of bromsulfalein at forty-five minutes was considered abnormal (employing 5 mg. per kg. of body weight).

Needle biopsies of the liver were performed in thirty selected cases to correlate function and histology. Liver biopsies were obtained with the "Vim-Silverman" needle using the intercostal approach.[8] There were no complications from this procedure. Sections were fixed in formalin and stained with hematoxylin and eosin in most instances. Glycogen stains were performed in six biopsies. A diagnosis of fatty liver was made when more than 10 per cent of the cells were fat laden. Criteria for the diagnosis of portal cirrhosis included periportal fibrosis, pseudolobulation, bile-duct proliferation and/or lymphocytic filtration with or without fat.

Those patients in whom laboratory or histologic evidence of liver dysfunction was found were placed upon a hepatic regimen consisting of a weighed diet of 300 to 400 gm. of carbohydrate, 100 to 175 gm. of protein and 50 to 100 gm. of fat unless obesity was present. Supplemental choline, methionine, protein hydrolysates, liver extract and therapeutic multivitamins were given selected patients. Insulin was administered when necessary.

TABLE I
RESULTS OF LIVER FUNCTION STUDIES

	Patients	
	No.	Per cent
Normal hepatic function	232	61.1
Hepatic dysfunction	148	38.9
Abnormal bromsulfalein	135	91.2
Positive cephalin-flocculation	115	77.7
Albumin/globulin ratio deviation	110	67.5
Cholesterol abnormality	74	50.0
Bilirubin abnormality	32	21.6

TABLE II
INFLUENCE OF AGE ON HEPATIC DYSFUNCTION IN DIABETES MELLITUS

Age	Total	Hepatic Dysfunction		Normal Function	
		Patients		Patients	
		No.	Per cent	No.	Per cent
Under 20	24	7	29.1	17	70.9
20–40	27	14	51.8	13	48.2
40–60	163	65	39.8	98	60.2
Over 60	166	62	37.3	104	62.7

TABLE III
INFLUENCE OF DURATION OF DIABETES MELLITUS ON HEPATIC DYSFUNCTION

Years	Total	Hepatic Dysfunction		Normal Function	
		Patients		Patients	
		No.	Per cent	No.	Per cent
Under 1	81	34	41.9	47	58.1
1–5	119	39	33.0	80	67.0
5–10	99	41	41.4	58	58.6
Over 10	85	28	32.9	57	67.1

RESULTS

One hundred forty-eight (38.9 per cent) patients had evidence of hepatic dysfunction and 232 (61.1 per cent) had normal hepatic function. Criteria for inclusion of a patient in the hepatic dysfunction group consisted of abnormality in at least two of the tests performed. (Table I.)

The incidence of hepatic dysfunction was proportionately the same in the sexes, 39.5 per cent of the males and 38.5 per cent of the females showing abnormal function. Age and duration of diabetes had no apparent influence on the incidence of hepatic dysfunction in this series (Tables II and III.)

The higher incidence between the ages of

twenty and forty may be attributed to a proportional increase in diabetic coma and infection in this group. On the other hand, the incidence of hepatic dysfunction seemed to increase moderately with the total insulin requirement (Table IV) and markedly with complicating pathologic states. (Table V.)

TABLE IV
INFLUENCE OF INSULIN REQUIREMENT

Units	Total	Hepatic Dysfunction		Normal Function	
		Patients		Patients	
		No.	Per cent	No.	Per cent
None	121	42	34.7	79	65.3
0–10	50	20	40.0	30	60.0
10–30	128	40	31.2	88	68.8
Over 30	81	46	56.7	35	43.3

TABLE V
INFLUENCE OF COMPLICATING PATHOLOGIC STATES ON INCIDENCE OF LIVER DYSFUNCTION IN DIABETES

	Total	Hepatic Dysfunction		Normal Function	
		Patients		Patients	
		No.	Per cent	No.	Per cent
Without complication	250	76	30.4	174	69.6
With complication	130	72	55.3	58	44.7
Vascular*	30	12	40.0	18	60.7
Obesity	40	18	45.0	22	55.0
Coma	22	14	63.6	8	36.4
Tuberculosis	14	9	64.3	5	35.7
Gangrene	24	19	79.2	5	20.8

* Peripheral, coronary and cerebral arteriosclerosis; symptoms referable to the vascular disease precipitated hospital admission of these patients

CORRELATION OF LIVER FUNCTION STUDIES AND HISTOLOGY

Eight patients of the thirty selected patients in whom needle biopsies of the liver were performed had normal hepatic function studies and twenty-two had varying degrees of abnormal function. Of those with normal function, five had normal livers and three had fatty metamorphosis on histologic examination. In the liver dysfunction group histologic examination revealed normal tissue in nine, fatty metamorphosis in five and portal cirrhosis in eight patients (Table VI.)

The correlation of function and histology depended upon the severity of the liver damage. With slight abnormalities there was a frequent dissociation while with major abnormalities close agreement was present. Of the patients with normal livers, three (21.4 per cent) had abnormal serum bilirubin levels, five (35.6 per cent) had significant bromsulfalein retention, six (42.7 per cent) had abnormal protein levels and five (35.6 per cent) had abnormal serum-cholesterol patterns. In those with fatty livers one (12.5 per cent) had an abnormal serum bilirubin level, three (37.5 per cent) had significant bromsulfalein retention, four (50.0 per cent) had abnormal cephalin-cholesterol flocculation tests, six (75.0 per cent) had abnormal protein levels and four (50.0 per cent) had abnormal serum-cholesterol patterns. Of the patients with cirrhotic livers, five (62.5 per cent) had abnormal serum bilirubin levels, eight (100 per cent) had significant bromsulfalein retention, five (62.5 per cent) had abnormal cephalin-cholesterol flocculation tests, seven (87.5 per cent) had abnormal protein findings and three (37.5 per cent) had abnormal cholesterol patterns.

Clinical evaluation revealed undernutrition with previous dietary inadequacy and alcoholism in each of the patients with abnormal histology. Two patients with fatty livers and seven with portal cirrhosis had enlarged livers. Spider angiomas were present in four of the patients with cirrhosis. Edema and ascites were absent.

THERAPY

Therapeutic results of the hepatic regimen in sixty-five patients of the group with

hepatic dysfunction have been analyzed. Five of these patients eventually succumbed to portal cirrhosis as confirmed at autopsy. Twenty-five selected from the needle-biopsy group and thirty-five evaluated on an outpatient basis without histologic study are still being followed-up.

TABLE VI

CORRELATION OF LIVER FUNCTION STUDIES WITH HISTOLOGY

Case No.	Age	Sex	Bilirubin mg. %	Bromsulfalein Per cent	Cephalin Flocculation Plus	Cholesterol mg. %		Total Protein gm. %	Albumin gm. %	Globulin gm. %	Liver Function Studies	Histology
						Total	Ester					
1	19	F	0	0	0	193	143	7.2	4.2	3.0	Normal	Normal
2	43	F	0	0.5	0	334	207	7.3	4.1	3.2	Normal	Normal
3	64	F	0.3	0	0	210	120	7.5	4.5	3.0	Normal	Normal
4	72	M	0	0	1	268	113	7.2	4.0	3.2	Normal	Normal
5	74	M	0.1	0.5	0	291	172	7.5	3.9	3.6	Normal	Normal
6	14	M	0.1	0	0	190	100	6.8	4.1	2.7	Normal	Fatty
7	46	M	0.3	0	1	283	158	7.5	3.8	3.7	Normal	Fatty
8	69	M	0.7	0	0	188	123	8.2	4.6	3.6	Normal	Fatty
9	19	F	0.2	0	2	384	205	8.6	3.9	4.7	Abnormal	Normal
10	51	F	0.3	0	4	283	70	7.2	3.6	3.6	Abnormal	Normal
11	52	F	0.7	9.0	0	300	190	6.9	2.8	4.1	Abnormal	Normal
12	47	M	0.3	0	2	308	191	6.2	3.3	2.9	Abnormal	Normal
13	60	M	0.35	11.0	2	549	263	6.5	3.2	3.3	Abnormal	Normal
14	65	F	1.2	1.0	2	239	177	6.5	2.6	3.9	Abnormal	Normal
15	68	M	1.6	24.0	4	229	109	7.8	3.4	4.4	Abnormal	Normal
16	70	M	0	11.5	1	260	176	5.8	2.5	3.3	Abnormal	Normal
17	71	F	1.2	17.5	0	131	64	5.9	2.5	3.4	Abnormal	Normal
18	15	M	0	0	2	164	42	8.6	3.1	5.5	Abnormal	Fatty
19	23	F	1.6	28.0	0	240	150	7.8	3.8	4.0	Abnormal	Fatty
20	59	F	0.1	0	2	268	141	7.2	3.3	3.9	Abnormal	Fatty
21	52	M	0.3	14.0	2	240	160	7.5	3.7	3.8	Abnormal	Fatty
22	61	F	0.8	22.0	2	266	170	6.8	2.9	3.9	Abnormal	Fatty
23	50	M	2.6	20.0	4	180	91	6.7	3.9	2.8	Abnormal	Portal cirrhosis and fat
24	59	M	2.0	25.0	3	276	158	8.5	4.0	4.5	Abnormal	Portal cirrhosis and fat
25	53	F	4.0	27.0	0	537	350	7.5	2.8	4.7	Abnormal	Portal cirrhosis and fat
26	56	F	0.5	13.5	1	290	160	5.5	2.9	2.6	Abnormal	Portal cirrhosis
27	58	M	1.0	14.5	4	229	109	7.8	3.4	4.4	Abnormal	Portal cirrhosis
28	57	M	0.1	18.0	2	226	138	7.1	2.5	4.6	Abnormal	Portal cirrhosis
29	61	M	0.3	32.0	1	183	106	7.2	2.7	3.5	Abnormal	Portal cirrhosis
30	79	M	2.0	10.0	2	188	103	6.2	2.1	4.1	Abnormal	Portal cirrhosis

A correlation of clinical features and therapeutic response (Table VII) suggested that hyperglycemia with glycosuria was secondary to liver disease in nine patients (Group I), liver disease was secondary to diabetes in forty-eight patients (Group II), and liver disease and diabetes were coincidental in two patients (Group III). A history of nutritional deficiency, alcoholism or exposure to hepatotoxins prior to the appearance of the diabetic syndrome and the disappearance of hyperglycemia with hepatotherapy and no insulin or a demonstration of insulin resistance placed a patient in Group I. A history of diabetes antedating clinical or subclinical evidence of hepatic disease and the demonstration of a need for insulin placed the patient in Group II. A history of diabetes with an independent history of hepatic damage placed a patient in Group III. Group III was

limited by the confines of the present study although a large number of diabetic patients develop intercurrent liver diseases.

In the histologically proven cirrhotic group two patients in Group I became aglycosuric on the hepatic regimen without insulin and two patients in Group I continued to have an insignificant glycosuria on the hepatic regimen without insulin. Five patients, two from Group III and three from Group II, continued to have hyperglycemia which was insulin responsive. Three patients in Group I had insulin-resistant hyperglycemia and glycosuria. Of the patients who succumbed, three were in Group I and one was in Group II.

TABLE VII

ETIOLOGIC CONSIDERATION FROM CORRELATION OF CLINICAL FEATURES AND THERAPEUTIC RESPONSE

	Histologic Studies Group			Clinic Group	Total
	Normal	Fatty Liver	Cirrhosis		
Group I					
Hyperglycemia secondary to liver disease	4	2	7	2	15
Group II					
Liver disease secondary to diabetes	5	6	4	33	48
Group III					
Liver disease and diabetes coincidental	..	..	2	..	2

With diabetes secondary to liver disease the ability to control hyperglycemia and glycosuria with hepatic therapy seemed to depend upon the severity of functional and histologic change. This emphasizes the necessity for early recognition of underlying liver disease and institution of therapy as soon as feasible. The following case history is illustrative:

Case No. 23. A fifty year old truck driver was first seen in the Jersey City Medical Center in July, 1942, with a chief complaint of "sore tongue." There was an associated weakness and a 31-pound weight loss. History revealed chronic alcoholism with an inadequate dietary intake for several years. Physical examination revealed glossitis, maculopapular eruption and liver enlargement to 5 cm. below the costal margin in the mid-clavicular line. Serology was negative, the hemogram was normal and urinalysis showed a 1 plus glycosuria. Fasting blood sugar was 154 mg. per 100 cc. and blood cholesterol was 245 mg. per 100 cc. An oral glucose tolerance curve showed a diabetic curve and the patient was placed on a diet of 170 gm. of carbohydrate, 70 gm. of protein and 50 gm. of fat with 10 units of protamine zinc insulin daily. He was also given multivitamins in therapeutic quantities. A twenty-four-hour quantitative urinalysis revealed no glucose and the patient's diet was accordingly increased to 200 gm. of carbohydrate, 100 gm. of protein and 90 gm. of fat. Insulin was discontinued and he was discharged to the Diabetic Clinic.

The patient did not report to the clinic; he consumed 1 to 2 pints of whiskey daily and ate poorly. He was again seen in November, 1946, at which time he was exhibiting icterus, hypovitaminosis and had an enlarged liver. His serum albumin was 3.6 gm. per 100 cc., serum globulin 3.2 gm. per 100 cc. and cephalin-cholesterol flocculation 4 plus. An oral glucose tolerance test resulted in a curve of the diabetic type. Fasting blood sugar levels fluctuated above 200 mg. per 100 cc. and there was a persistant 4 plus glycosuria. He was placed on a diet of 300 gm. of carbohydrate, 100 gm. of protein and 70 gm. of fat with multivitamins, methionine and 30 units of insulin daily. With this therapy glycosuria diminished and glucose tolerance gradually returned to normal. His hepatic status improved as evidenced by a cephalin-cholesterol flocculation of 2 plus, a disappearance of icterus and a decrease in hepatomegaly. The patient felt well and was discharged from the hospital.

He resumed his alcoholic habits and discontinued his diet. On rehospitalization in February, 1948, he was malnourished and his liver was again palpable 5 cm. below the right costal margin in the mid-clavicular line. The fasting blood sugar was 250 mg. per 100 cc. and urinalysis showed a 4 plus glycosuria. Twenty-four-hour quantitative glycosuria was 12 gm. Serum bilirubin was 2.6 mg. per 100 cc., bromsulfalein test showed 20 per cent retention, serum albumin was 3.9 gm. per 100 cc., serum globulin was 2.8 gm. per 100 cc., cephalin-cholesterol flocculation was 4 plus, total serum cholesterol was 180 mg. per 100 cc. and cholesterol esters were 90 mg. per 100 cc. Thymol turbidity was 2.0 units and alkaline phos-

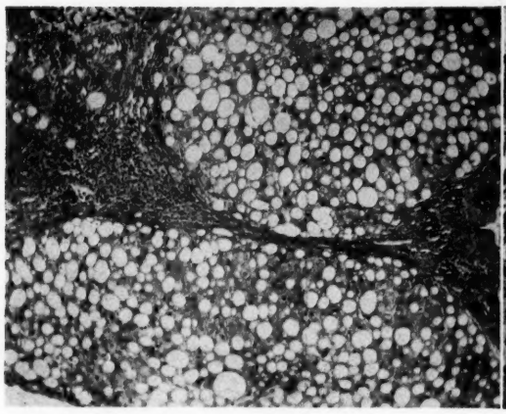

FIG. 1. Marked fatty metamorphosis with periportal fibrosis, pseudolobulation and lymphocytic infiltration. Pathologic diagnosis: portal cirrhosis.

FIG. 2. Periportal fibrosis, pseudolobulation, bile duct proliferation and lymphocytic infiltration without fat. A third biopsy showed decrease in lymphocytes.

phatase was 3.8 units. A needle biopsy of the liver showed portal cirrhosis with marked fatty metamorphosis. (Fig. 1.) He was placed on a diet of 300 gm. of carbohydrate, 175 gm. of protein and 70 gm. of fat, with therapeutic multivitamin capsules, crude liver extract and 2 gm. each of methionine and choline three times daily. On this regimen the twenty-four-hour quantitative glycosuria was reduced to 6 gm. Repeat liver function studies in thirty days showed a serum bilirubin of 1.0 mg. per 100 cc., cephalin-cholesterol flocculation 1 plus, bromsulfalein retention 2 per cent, total serum cholesterol 188 mg. per 100 cc. and cholesterol esters 135 milligrams per 100 cc. A repeat biopsy showed portal cirrhosis without fat. (Fig. 2.) Increasing doses of insulin were given (up to 90 units daily) without effect on glycosuria. He was discharged to the Hepatic Clinic without insulin and is being followed-up.

Patients with cirrhosis and without fatty changes have had functional improvement as illustrated by the following case history:

Case No. 27. A fifty-eight year old laborer was referred from the Diabetic Clinic where he had been followed six years because of progressive weakness. History revealed chronic alcoholism with a poor dietary intake for fifteen years. Physical examination revealed hepatomegaly, splenomegaly and the presence of spider angiomas. Liver function studies confirmed a diagnosis of hepatic dysfunction. Serum bilirubin was 1.0 mg. per 100 cc., the bromsulfalein test showed 14.5 per cent retention in forty-five minutes, serum albumin was 3.4 gm. per 100 cc., serum globulin was 4.4 gm. 100 cc., cephalin-cholesterol flocculation was 4 plus, thymol turbidity was 4.0 units, total serum cholesterol was 229 mg. per 100 cc. and cholesterol esters were 109 mg. per 100 cc. Glucose tolerance curve showed a diabetic response. Increasing doses of insulin had little effect on hyperglycemia and glycosuria. A needle biopsy of the liver showed portal cirrhosis. (Fig. 3.) The patient was placed on a hepatic regimen with a diet of 300 gm. of carbohydrate, 150 gm. of protein and 70 gm. of fat, therapeutic multivitamins, 2 gm. each of methionine and choline three times daily and liver extract. On this regimen his twenty-four hour quantitative glycosuria was 9 gm. and the patient improved subjectively. A repeat biopsy of the liver one month later showed no essential change. At this time his liver function studies showed improvement with no bromsulfalein retention, serum albumin of 4.3 gm. per 100 cc., serum globulin of 3.4 gm.

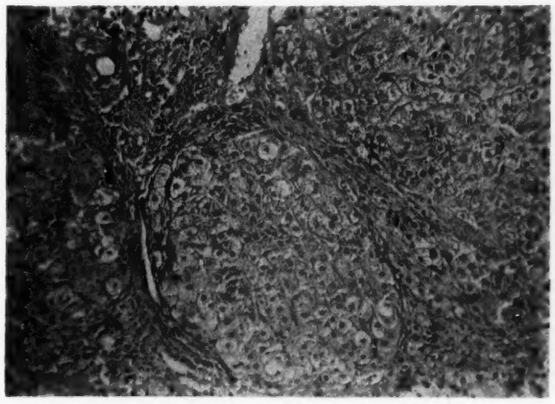

FIG. 3. Pseudolobulation, periportal fibrosis, lymphocytic infiltration. Pathologic diagnosis: portal cirrhosis.

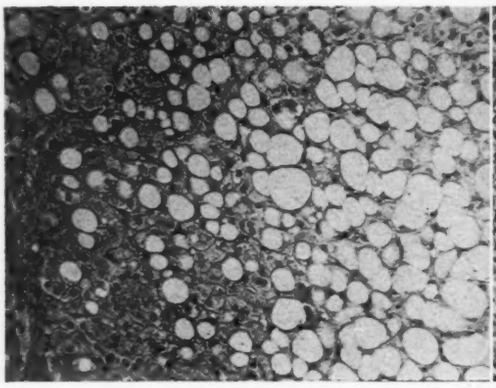

FIG. 4. Moderate fatty metamorphosis without fibrosis.

FIG. 5. Normal liver after one month of therapy.

per 100 cc. and a 1 plus cephalin-cholesterol flocculation.

Therapy of fatty livers associated with hyperglycemia and glycosuria has provided the best field for therapeutic study. Persistence of carbohydrate intolerance after the disappearance of fat and reversal of biochemical abnormalities eliminates the hepatic factor as a major etiologic basis. Restoration of carbohydrate tolerance along with reversal of histologic and biochemical changes directly implicates the hepatic abnormality as etiologic in hyperglycemia and glycosuria. The following case history is illustrative:

A fifty-nine year old fireman with a history of alcoholism and episodes of poor nutrition for thirty years was hospitalized for delirium tremens in 1948. Prior to admission he had eaten poorly and consumed an average of 1 quart of whiskey and 1 quart of wine each day for a month. Physical examination revealed a smooth, red, atrophic tongue and hepatomegaly. A blood sugar level was 149 and urine glycosuria 2 plus recorded during his delirium. After the acute episode hyperglycemia and glycosuria disappeared.

He was readmitted in 1949 after returning to his previous habits. Following the clearing of his delirium tremens he had some polyuria and polydipsia. His fasting blood sugar was 184 mg. per cent with a 4 plus glycosuria. Examination revealed liver enlargement to 4 cm. below the costal cage. Liver studies showed a serum bilirubin of 3.6, no bromsulfalein retention, serum albumin 3.4 gm. per cent, serum globulin 4.1 gm. per cent, cephalin-flocculation test negative, thymol turbidity 2.0, cholesterol 268 mg. per cent and cholesterol ester 116 mg. per cent. A glucose tolerance test revealed a diabetic curve. A needle biopsy of the liver revealed moderate fatty metamorphosis. (Fig. 4.) He was given a diet of 350 gm. of carbohydrate, 120 gm. of protein and 80 gm. of fat with therapeutic multivitamins and 6 gm. of choline daily. On this regimen his hyperglycemia and glycosuria disappeared and carbohydrate tolerance returned to normal. A repeat needle biopsy of the liver in one month revealed normal liver tissue. (Fig. 5.) Biochemical function studies at this time showed a normal serum bilirubin, serum albumin 3.5 gm. per cent and serum globulin 3.3 gm. per cent. Hepatomegaly and symptoms disappeared with treatment.

Hepatic therapy resulted in improvement in carbohydrate tolerance in each of the patients with normal histology and abnormal function. Four have not required insulin with such therapy. The following case history is illustrative:

Case No. 15. A sixty-eight year old laborer was hospitalized during October, 1947, with complaints of fatigue and anorexia. One year previously he had been placed on a diet for control of polyuria and polydipsia. Past history revealed consumption of large quantities of alcohol and a poor food intake for several years. Physical examination revealed peripheral arteriosclerosis and calcareous aortic stenosis with compensated heart disease. Laboratory studies showed hyperglycemia and glycosuria, a serum bilirubin of 1.6 mg. per 100 cc., bromsulfalein retention of 24 per cent, cephalin-cholesterol flocculation of 4 plus, serum albumin 3.2 gm.

per 100 cc., serum globulin 4.1 gm. per 100 cc., total serum cholesterol 242 mg. per 100 cc. and cholesterol esters of 138 mg. per 100 cc. A needle biopsy of the liver showed normal histology. The patient was placed on a hepatic regimen and his insulin requirement was reduced from 15 units on a restricted carbohydrate intake to zero on a 300-gm. carbohydrate intake. A repeat battery of liver function studies eight months later revealed reduction of serum bilirubin to 0.7 mg. per 100 cc. and bromsulfalein retention to 7.5 per cent. His cephalin-cholesterol flocculation was negative, serum albumin was 3.6 gm. per 100 cc. and serum globulin was 3.8 gm. per 100 cc.

The thirty-five clinic patients were re-evaluated after one year or more of hepatic therapy. Repeat liver function studies showed a return to normal function in twenty-four (68.4 per cent), improvement with some persisting abnormality in six (17.1 per cent) and no improvement in five (14.5 per cent). Insulin dosage remained the same in seventeen (48.6 per cent), decreased in fifteen (47.8 per cent) and increased in three (8.6 per cent). Fourteen obese patients were placed on a modified hepatic diet (1,800 calories) with a resulting significant weight reduction in eight (57.1 per cent), no change in four (28.6 per cent) and an increase in weight in two (14.3 per cent). An obese patient who lost 22 pounds and reversed her previously abnormal function studies and became aglycosuric without insulin was believed to have liver dysfunction producing the hyperglycemia and glycosuria.[9] In the non-obese group there were no significant weight changes. Three clinic patients reversed their function studies and became aglycosuric without insulin and thirty-one continued to require insulin. Liver function studies returned to normal in twenty of the latter group. The following case history is illustrative:

A nine year old school boy was admitted to the hospital in January, 1946, in diabetic coma. Past history revealed onset of diabetic symptoms one month previously following an upper respiratory infection. Examination revealed marked undernutrition. The patient responded to therapy and subsequently was controlled on a diet with 30 units of protamine zinc insulin. Following discharge his mother gradually diminished his insulin dosage until July, 1946, at which time he was aglycosuric on 3 units of protamine zinc insulin daily. At this time he was seen in the Diabetic Clinic and examination revealed undernutrition, general lassitude and a liver enlarged to the iliac crest. Liver function studies revealed a 2 plus cephalin-cholesterol flocculation reaction, 25.0 per cent retention of bromsulfalein, an icterus index of 15.2 units, serum albumin 5.2 gm. per 100 cc., serum globulin 1.9 gm. per 100 cc. and a total cholesterol of 295.4 mg. per 100 cc. Fasting blood sugar was 120 mg. per cent. A twenty-four-hour quantitative urinalysis showed 3.0 gm. of glucose. Five units of crystalline insulin produced a hypoglycemic reaction. He was placed on a diet of 300 gm. of carbohydrate, 125 gm. of protein and 60 gm. of fat with therapeutic multivitamins and methionine. Within twenty-five days the liver was no longer palpable and all hepatic function studies had become normal. On a diet of 200 gm. of carbohydrate, 100 gm. of protein and 70 gm. of fat, he required 30 units of insulin for control. At this writing he requires 25 units of insulin on the same diet, has no hepatic dysfunction which can be demonstrated, is well and has gained 15 pounds.

This patient is typical of the juvenile diabetic whose liver dysfunction is a complicating factor. In this instance the liver dysfunction was associated with a decrease in insulin requirement. From the over-all insulin changes in the clinic group, it was shown that secondary liver damage may have either no effect or may decrease or increase the insulin requirements of the diabetic patient.

COMMENT

Identification of the phosphorylating mechanism in carbohydrate metabolism in the liver has directly focused attention upon the relative role of this organ in producing disturbances in the regulation of carbohydrate metabolism. Liver disease impairs glycogen storage and may lead to either hypoglycemia or hyperglycemia although most patients with primary hepatic disorders have neither. Glucose tolerance may be normal or abnormal.[10] The severity or

selectivity of the pathologic process in the liver may determine whether there will be a carbohydrate disturbance. Further studies are needed to determine the relative influence of anatomic and biochemical disturbances in the liver in producing disturbances in the regulation of carbohydrate metabolism.

The control or correction of the hyperglycemia and glycosuria secondary to liver disease depends upon early diagnosis and proper treatment. Recognition of "hepatogenic diabetes" is only possible by routinely evaluating the diabetic patient for clinical stigmas or functional abnormalities indicative of liver disease. Assay of hepatic function can be made by using the bromsulfalein and cephalin-cholesterol flocculation tests. When liver dysfunction is suspected, a suitable battery of liver function studies should be obtained; and, in selected instances, needle biopsy of the liver may be performed as a diagnostic adjunct. The significance of liver dysfunction in the disturbance of carbohydrate metabolism producing the diabetic syndrome may be evaluated finally by the results of hepatotherapy.

Attention should also be directed to the care of the diabetic patient with liver dysfunction secondary to deficient nutrition. Although the efficacy of high carbohydrate, high protein and high vitamin intake in both liver disease and diabetes is established, the attempt to control glycosuria by maintaining a low carbohydrate and protein intake is still responsible for nutritional deficiencies in many patients. These deficiencies may lead to a fatty or necrotic liver and ultimately to cirrhosis.[11] The functional or histologic changes in the liver furnish a basis for corrective therapy in such patients. It is evident that while continued emphasis must be placed upon the necessity for avoidng both hyperglycemia and glycosuria in caring for the diabetic patient, equal stress must be placed on providing for associated nutritional defects. The incidence and significance of hepatic dysfunction and diabetes will vary with the nutritional backgrounds of the patient studied. When hepatic dysfunction is due to a complicating disease process, the need for restoring hepatic integrity from both immunologic and metabolic points of view is urgent.

SUMMARY

1. A battery of hepatic tests was performed in 380 patients with diabetes to determine the incidence of liver dysfunction and its relationship to etiology of manifest hyperglycemia with glycosuria.

2. One hundred forty-eight of those studied (38.9 per cent) were found to have evidence of liver dysfunction. Of 130 patients with complications, 55.3 per cent had hepatic dysfunction; 30.4 per cent of those without evident complications had abnormal hepatic studies. Gross dietary and insulin insufficiencies were accompanied by liver dysfunction more frequently; age, sex and duration of diabetes had no influence on the frequency of liver involvement.

3. Thirty selected diabetic patients were subjected to needle biopsy of the liver. Of eight with normal hepatic function five had normal livers and two had fatty metamorphosis on histologic examination. Of 22 with liver dysfunction, histologic examination revealed normal tissue in nine instances, fatty metamorphosis in five instances and portal cirrhosis in eight instances.

4. Sixty-five patients with the diabetic syndrome and evidence of hepatic dysfunction have been followed-up for periods of more than twelve months on a hepatic regimen. Correlation of history, physical examination, function studies and therapeutic response suggests hepatic dysfunction was responsible for abnormal carbohydrate metabolism in fifteen patients, liver dysfunction was secondary to diabetes in forty-eight patients and liver disease and diabetes were coincidental in two patients. One patient had diabetes and hepatic dysfunction which were attributed to obesity.

5. Hepatic studies aid in the evaluation of patients with a provisional diagnosis of diabetes mellitus and constitute a good

method of periodically evaluating the degree of control of diabetic patients.

6. Liver dysfunction may occasionally produce the diabetic syndrome or be secondary to it. In eleven patients in whom hepatic disease was believed to be the cause of hyperglycemia with glycosuria, hepatic therapy without insulin resulted in improvement in the hepatic dysfunction and carbohydrate disturbance. Of thirty-five clinic patients with liver dysfunction secondary to diabetes, the hepatic abnormality and carbohydrate tolerance improved with hepatic therapy and insulin in thirty.

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Clinical, Functional and Histologic Studies in Laennec's Cirrhosis of the Liver*

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THIS report is a study of the clinical, functional and histologic findings in Laennec's cirrhosis of the liver. During the past decade liver biopsy technics have offered a useful method for the investigation of histologic changes in the liver, along with parallel studies of the clinical and functional states in patients with disease of the liver.[1–6] Within recent years there has been comment on the correlation between structure and function in liver disease, some authors reporting such a correlation[7–10] and others not supporting this view.[11–15] The results to be presented indicate that under the conditions of this study there was no good correlation between the histologic appearance of the liver and either the clinical state of the patient or the laboratory tests for liver function in Laennec's cirrhosis of the liver.

METHODS

The data to be presented were derived from sixty-two patients with Laennec's cirrhosis of the liver presenting varying degrees of clinical severity of illness. All patients were investigated with regard to history, physical findings, conventional liver function tests and liver biopsy. Alcoholism and a poor dietary intake were noted in all patients. The significant symptoms were the presence of jaundice, weight loss and gastrointestinal complaints. The chief physical findings included jaundice, vascular "spiders," palpable liver and spleen, "liver palms," wasting, edema and ascites.

The tests of liver function employed were serum bilirubin, cephalin-flocculation test, serum cholesterol-cholesterol ester partition, serum alkaline phosphatase (Bodansky units), thymol turbidity, serum albumin-globulin partition and bromsulfalein dye retention.

Biopsy specimens were obtained with the Vim-Silverman needle[16] employing an approach in the right mid-axillary line in the ninth or tenth interspace. Specimens were fixed in formalin (10 per cent) and stained with hematoxylin-eosin. While the histologic picture of the liver as obtained from a tiny fragment of liver tissue may not represent the true state of the organ in its every detail, it is believed that in diffuse processes affecting the liver a reasonably good histologic estimate may be derived from such material. Comparison of such specimens with postmortem material usually shows good agreement.

Patients were grouped according to their respective clinical states at the time of study. The following classification was used:

Group I. Most of these seventeen patients had mild to severe gastrointestinal symptoms, weakness and nutritional deficiency. They had never shown severe hepatic insufficiency with edema, ascites or coma. In some instances patients had palpable livers and "liver palms" as the sole abnormalities noted in the course of a routine examination for an unrelated complaint.

Group II. These sixteen patients had symptoms similar to those in group I. However, they had ascites which required paracentesis. All were bedridden, poorly nourished and seriously ill.

Group III. These fourteen patients had a diuresis with loss of ascites and edema within one to two months prior to the time of the study. They had shown marked clinical improvement during this time, with gains in weight, strength and appetite and with clinical evidence of subsiding liver disease.

Group IV. These fifteen patients died in hepatic failure, with ascites, wasting and coma.

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This group has been considered to represent the end stage of progressive liver disease. No patients have been included in whom liver disease was a secondary cause of disability or death. Patients with death from hematemesis have been excluded because bleeding from esophageal varices is not considered a necessary consequence of liver insufficiency as such but rather an anatomic accident.

The data have been recorded in tabular form, showing the significant features in the clinical states, the laboratory tests and histologic descriptions observed at the same times.

Each histologic characteristic (fat, fibrosis, necrosis, inflammatory cellular infiltration) has been graded 0 to 4 plus, depending upon the extent of the process. Necrosis has been diagnosed when liver cells have shown disruption of cellular organization and eosinophilia and pyknosis of nuclei. Liver cell regeneration has been identified by the presence of nests of budding hyperchromatic liver cells. This has been graded 0 and + to indicate its presence.

At the bottom of each table is a summary. Under "physical signs" the number of positive findings noted in each category is represented by the numerator and the number of patients in the group by the denominator. This technic has been used for "regeneration" under "histology." The other figures represent means of the respective categories. Each table has an accompanying plate of photomicrographs, showing representative fields (100 ×) of the respective liver biopsies.

RESULTS

Group I. In Table 1 and Figure 1 are noted the data for Group 1. The symptomatology was characterized by anorexia and gastrointestinal complaints. A few patients had recurrent hematemeses which they had survived. Jaundice was not frequent. The liver was palpable in all patients from 1 to 8 cm. below the right costal margin. The spleen was palpable in about half the patients. Vascular "spiders" and "liver palms" were seen often. Clinical evidence of severe cachexia was infrequent.

The laboratory tests showed a wide variety of changes. Marked bile pigment retention was uncommon. The cephalin-flocculation reaction was positive in more than half the patients. The cholesterol-cholesterol ester partitions were usually normal. Bromsulfalein retention was abnormal in most patients. Alkaline phosphatase values were not remarkable. Thymol turbidity levels were increased in most of the patients tested. Serum albumin levels were reduced in most patients but the change was marked in only one patient (Case 17). Serum globulin elevation was noted in some patients. In general, the degree of serum protein change was not marked. In summarizing the laboratory findings, the cephalin-flocculation, thymol turbidity and bromsulfalein excretion tests and the serum albumin levels were most frequently abnormal.

Table 1 summarizes the histologic changes and Figure 1 shows representative photomicrographs. Examination of these specimens discloses varying degrees of change. It is apparent that a most advanced histologic lesion may be seen in a patient with minimal laboratory and clinical evidence of liver disease (Case 3). On the other hand, Case 17 with Wernicke's encephalopathy and wasting showed rather mild histologic changes but marked functional abnormalities, with hypoalbuminemia, increased bromsulfalein retention, positive cephalin-flocculation and thymol turbidity tests.

The predominantly fatty lesion could not be correlated with any particular clinical or laboratory pattern. Case 9 showed mild jaundice and 2 plus cephalin-flocculation reaction in association with severe fatty change. This patient had been deeply jaundiced during the previous month following a long alcoholic spree. Case 12, with an equally fatty liver, had no jaundice but showed a positive cephalin-flocculation reaction, reduction in serum cholesterol, minimal bromsulfalein retention and reduction in serum albumin.

In summarizing the data in this group, it would seem that a wide range of histologic changes may be seen in these patients. This may be associated with mild to moderate abnormalities in liver function tests. The histologic lesion does not seem

TABLE I

GROUP I

Case No.	Age	Sex	Physical Signs								Laboratory Tests							Histology					
			Jaundice	Edema	Ascites	Palpable Liver	Palpable Spleen	Vascular "Spiders"	"Liver Palms"	Cachexia	Bilirubin	Cephalin-Flocculation	Thymol Turbidity	BSP	Alkaline Phosphatase	Cholesterol/Ester	Albumin/Globulin	Fat	Fibrosis	Necrosis	Regeneration	Cellular Infiltration	Course
1	48	F	0	0	0	+	+	+	+	+	0.4	0	7.0	7	4.2	204/122	3.4/2.8	3+	1+	0	0	1+	I*
2	48	M	0	0	0	+	0	0	+	0	1.5	4+	8.0	46	...	247/105	3.5/3.1	3+	3+	1+	+	1+	I
3	49	M	0	0	0	+	+	0	+	0	0.8	0	5.0	18	4.0	...	4.2/1.1	3+	3+	1+	+	2+	U
4	60	M	0	0	0	+	+	+	+	0	0.5	2+	6.5	..	1.2	164/112	3.9/2.6	3+	2+	0	0	1+	I
5	46	M	0	0	0	+	+	0	0	0	0.5	0	....	2	5.8	173/78	4.7/3.1	0	3+	0	0	3+	I
6	37	M	+	0	0	+	+	+	+	0	2.2	3+	10.7	..	...	256	3.4/5.2	0	3+	0	+	1+	I
7	40	M	0	0	0	+	0	+	+	0	2.1	2+	8.0	30	3.9	...	3.6/4.2	3+	3+	0	+	3+	I
8	46	F	0	0	0	+	+	+	+	0	0.5	4+	....	15	...	192/139	4.9/2.7	1+	2+	0	0	3+	I
9	39	M	+	0	0	+	+	0	+	0	2.8	2+	4.0	0	4.6	...	3.9/2.8	4+	1+	1+	0	1+	I
10	40	M	0	0	0	+	0	0	0	0	1.4	0	...	20	5.1	...	4.7/3.2	3+	1+	1+	0	2+	I
11	51	F	0	0	0	+	0	0	0	+	1.3	2+	1.5	30	7.8	...	3.2/2.0	4+	3+	0	+	1+	—
12	50	F	0	0	0	+	0	+	0	0	0.5	3+	....	10	1.5	128/66	3.2/2.9	4+	1+	0	0	1+	D
13	56	M	+	0	0	+	0	+	0	0	3.7	4+	22.0	65	3.6	273/151	3.3/4.2	0	3+	0	+	3+	—
14	37	F	0	0	0	+	+	+	+	0	1.2	0	....	..	2.0	278/215	3.9/2.2	4+	2+	0	+	3+	I
15	37	M	0	0	0	+	0	0	0	0	0.4	.....	....	35	...	270/192	5.1/2.4	1+	1+	1+	0	1+	I
16	46	M	0	0	0	+	0	0	0	0	0.5	0	....	15	...	245/167	3.3/4.3	0	2+	1+	0	3+	U
17	35	F	0	0	0	+	0	0	0	+	0.5	2+	9.5	33	...	...	2.4/1.9	0	1+	1+	+	3+	I

* I—Improved D—Died
U—Unimproved —No follow-up
These notations have been used in all tables.

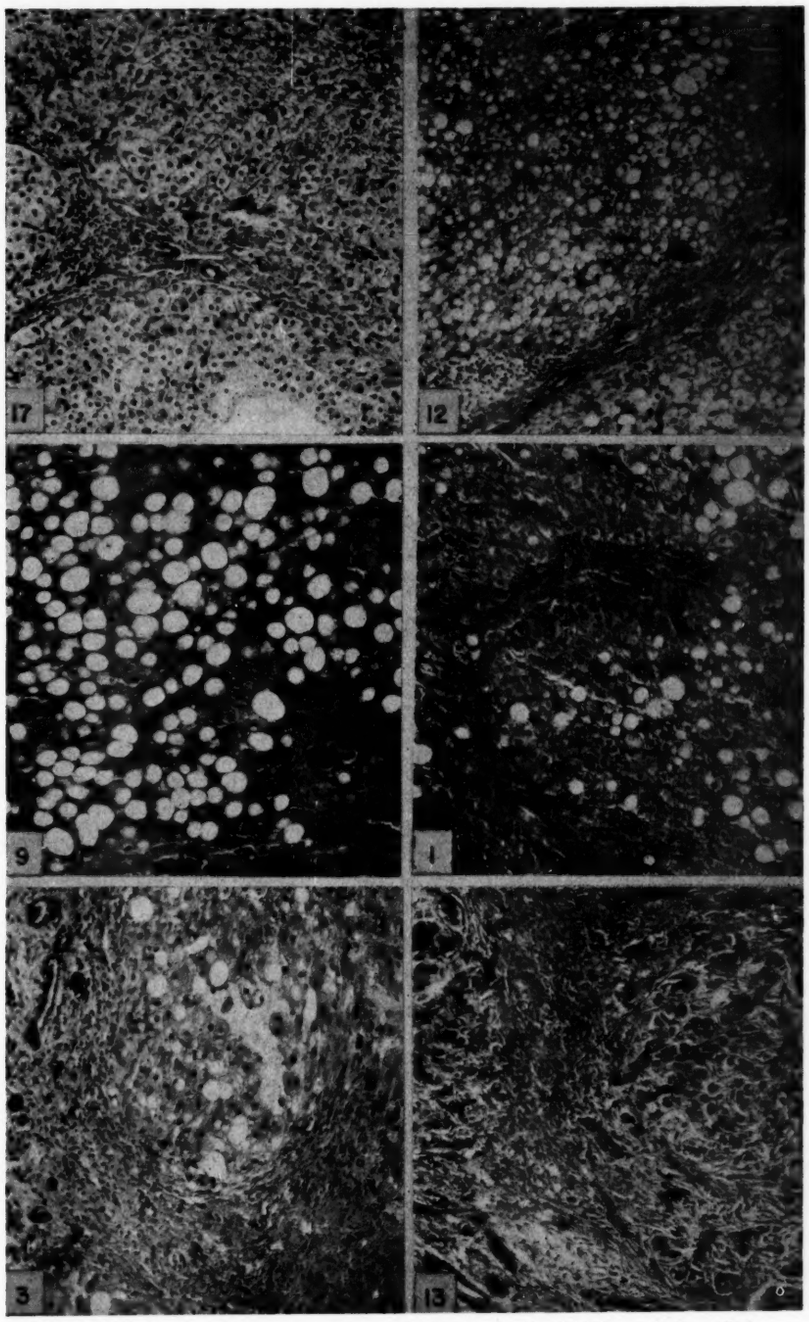

FIG. 1. Liver biopsies from six patients in Group I; "mild" hepatic insufficiency; hematoxylin and eosin stain, × 100.

to be correlated with the clinical appearance of the patient or the laboratory tests for liver function.

Group II. In Table II and Figure 2 are shown the data from patients whose illness was severe. These patients had ascites which required paracentesis. Symptomatically they had complaints similar to those in group I but these were more marked. Abdominal pain, anorexia and cachexia were more evident than in group I. Clinical jaundice was common. The liver and spleen were not so readily palpated here as in group I. This may have been due to the presence of ascites. Vascular "spiders" and "liver palms" were common. Hyperbili-

TABLE II
GROUP II

Case No.	Age	Sex	Physical Signs								Laboratory Tests							Histology					
			Jaundice	Edema	Ascites	Palpable Liver	Palpable Spleen	Vascular "Spiders"	"Liver Palms"	Cachexia	Bilirubin	Cephalin-Flocculation	Thymol Turbidity	BSP	Alkaline Phosphatase	Cholesterol/Ester	Albumin/Globulin	Fat	Fibrosis	Necrosis	Regeneration	Cellular Infiltration	Course
18	40	M	0	+	+	+	0	+	+	+	1.8	3+	....	40	9.0	...	4.1/3.4	2+	4+	0	+	1+	I*
19	61	M	+	+	+	0	0	0	+	+	0.9	3+	....	50	1.7	179/137	3.0/3.6	0	4+	0	0	4+	I
20	58	M	0	+	+	0	0	+	0	+	6.1	4+	....	45	8.5	...	2.6/3.8	0	3+	0	0	4+	I
21	58	M	+	+	+	0	0	+	+	+	1.7	4+	13.3	38	6.4	202/135	3.3/3.9	3+	4+	0	+	3+	I
22	55	F	0	0	+	+	0	0	0	0	0.8	2+	....	32	7.0	118/81	2.7/2.7	2+	2+	0	0	1+	I
23	73	M	0	+	+	+	+	0	+	+	0.5	4+	7.0	25	2.1	155	2.9/5.0	0	2+	0	+	3+	D
24	33	F	+	+	+	+	0	+	+	+	2.4	4+	....	40	6.2	197/112	3.0/3.5	0	2+	1+	+	2+	I
25	53	M	+	+	+	0	0	+	+	0	3.2	0	....	..	....	208/93	2.2/2.7	0	2+	0	0	2+	D
26	53	M	0	+	+	+	0	+	+	0	0.5	3+	6.1	22	....	...	3.0/4.6	0	4+	1+	+	1+	I
27	63	F	+	+	+	+	+	0	0	+	1.5	0	.....	15	1.2	167	3.9/3.2	0	2+	1+	0	3+	I
28	42	M	0	+	+	+	0	0	0	0	1.6	.....	....	30	2.0	250/135	3.2/3.9	0	3+	0	0	3+	U
29	70	M	+	+	+	+	0	0	+	+	11.2	2+	.....	..	22.5	125/81	3.9/3.2	1+	4+	0	+	4+	I
30	60	M	0	+	+	+	0	0	0	0	0.5	2+	14.0	37	16.6	246/155	2.8/4.1	0	1+	0	0	3+	D
31	59	M	0	+	+	0	0	0	+	+	1.0	2+	....	20	2.2	...	2.3/5.2	1+	3+	0	+	2+	I
32	57	M	+	+	+	0	0	0	0	+	2.8	4+	....	45	12.1	...	2.5/4.5	0	3+	0	+	3+	I
33	54	M	+	0	+	+	+	+	+	0	1.1	3+	.....	..	4.7	...	2.8/3.0	0	1+	0	0	1+	I

*See explanation in Table 1, page 302.

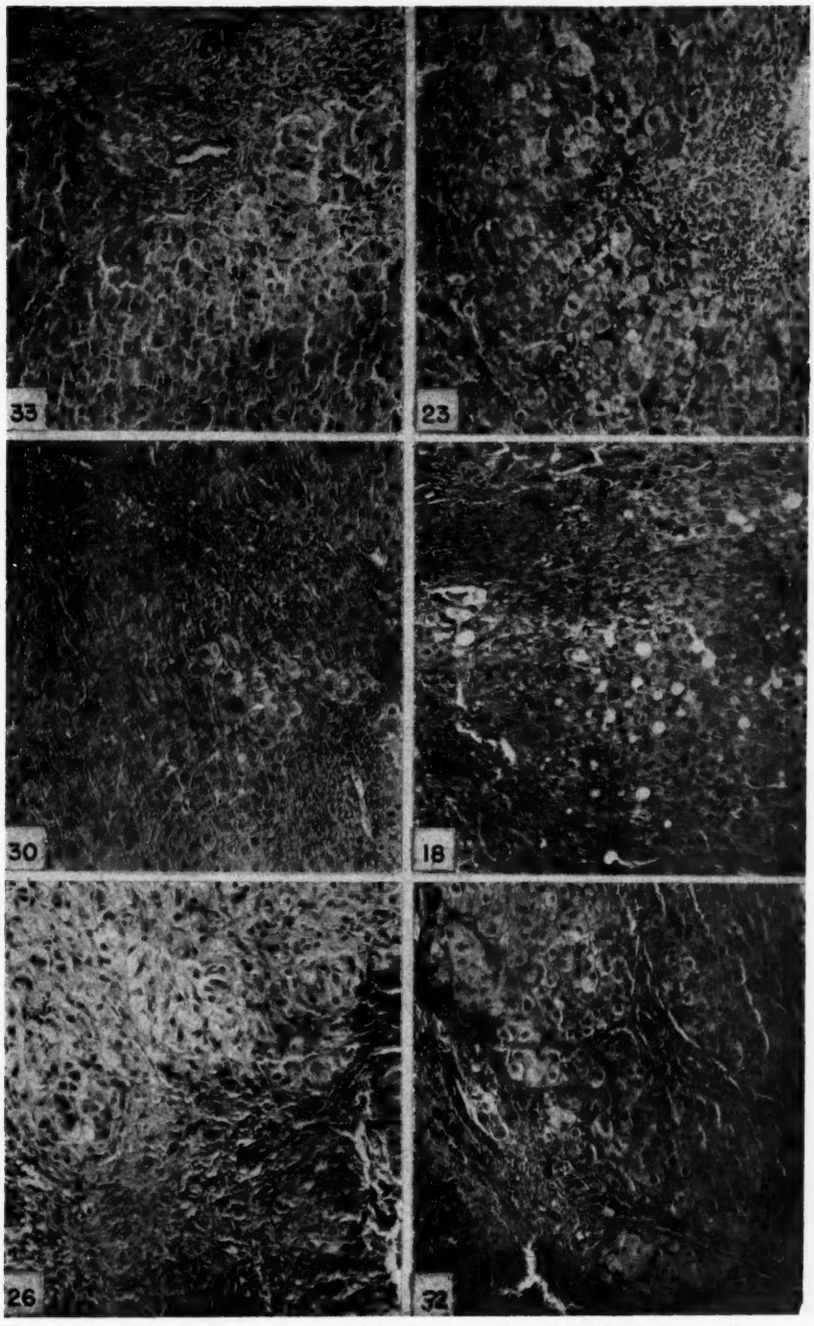

FIG. 2. Liver biopsies from six patients in Group II; "marked" hepatic insufficiency; hematoxylin and eosin stain, × 100.

rubinemia occurred often. The cephalin-flocculation reaction was positive in all but five patients tested. The blood cholesterol was reduced in three of ten patients. All patients tested had increased bromsulfalein retention. Only three patients had markedly raised alkaline phosphatase levels above 10. All but one patient had reduction in the serum albumin values. Elevation in the serum globulin was common.

In general, the laboratory tests in these seriously ill patients showed abnormalities in albumin-globulin partition, bromsulfalein retention, cephalin-flocculation reaction and bilirubin. The changes in all of these tests were greater than those noted in group I.

The quantitative changes in serum albumin were especially marked.[17]

The histologic changes in this group of patients are detailed in Table II and Figure 2. Wide variations in degree of lesion are noted. For example, Case 23 showed relatively mild changes histologically in contrast to Cases 32 and 26 with far advanced lesions. Other patients showed changes in between these extremes. In comparing the clinical states and laboratory tests of these patients with their respective histologic lesions the advanced lesion and minimal lesion might occur, respectively, in patients who were equally disabled clinically and whose function tests were similarly disturbed.

It is noteworthy that Cases 23 and 30, who had relatively mild histologic lesions, subsequently died of hepatic insufficiency. Cases 32, 26 and 18 who had severe histologic lesions had diureses and improved markedly.

Group III. In this group are included patients who had had diuresis with loss of edema and ascites and had gained weight and strength. All patients had been seriously ill before the diuresis. During the period of ascites they had appeared similar to the patients in group II. Indeed, their laboratory data, shown in Table III, represent striking changes toward normal when compared with data obtained several months earlier. At the time of the study, one to two months after diuresis, they were markedly improved and relatively symptom-free.

Physical examination showed jaundice to be uncommon. The liver and spleen were palpated in most patients. Spider angiomas and "liver palms" were very common. The laboratory tests showed hyperbilirubinemia to be infrequent, and when it was present it was mild. The cephalin-flocculation reaction was usually positive. The blood cholesterol and thymol turbidity values were determined in too few patients to be noteworthy. The degree of bromsulfalein retention was mild when present. Alkaline phosphatase values were not remarkable. The serum albumin levels were reduced in many patients but were not markedly lowered. Serum globulin elevation was present in some patients.

In considering the histologic lesions of this group, reference is made to Table III and Figure 3. With the exception of Case 39 all of the sections showed advanced fibrosis with architectural distortion, bile duct proliferation, abnormally large liver cells, etc. These changes were similar to those seen in group II. In two patients a moderate amount of fatty change was noted (Cases 42 and 46). It is of interest that although the histologic lesions seen in group II were very similar to those seen in group III, the clinical states of the respective patients as well as their laboratory tests were so different. In group II are patients seriously ill from liver insufficiency and in Group III are patients who have recently recovered from that state. This contrast in respective clinical and "functional" states on the one hand and similarity of liver histology on the other emphasizes the absence of correlation between the liver histology and the clinical and "functional" behavior of patients with this disease. All of these patients (group III) have remained in good health up to the present time for periods of six to twenty-four months.

Group IV. In Table IV are shown the data on patients who succumbed to hepatic insufficiency. In these patients a period of illness with progressive wasting, edema and ascites usually preceded coma and death. These patients had symptoms similar to those noted in other groups. Their physical findings were as found in group II.

Clinical jaundice was seen in all patients. The laboratory data were obtained within one week of death. The degree of increased serum bilirubin was most marked in this group. Cephalin-flocculation reactions were all positive. Serum cholesterol, bromsulfalein retention and thymol turbidity studies were few in this group but were abnormal when performed. Alkaline phosphatase values were normal. Serum albumin and globulin changes were usually marked.[17]

The laboratory studies in these patients showed changes similar to those noted in

TABLE III

GROUP III

Case No.	Age	Sex	Physical Signs								Laboratory Tests							Histology					
			Jaundice	Edema	Ascites	Palpable Liver	Palpable Spleen	Vascular "Spiders"	"Liver Palms"	Cachexia	Bilirubin	Cephalin-Flocculation	Thymol Turbidity	BSP	Alkaline Phosphatase	Cholesterol/Ester	Albumin/Globulin	Fat	Fibrosis	Necrosis	Regeneration	Cellular Infiltration	Course
34	50	M	0	0	0	+	+	+	+	0	0.1	2+	...	0	2.0	...	3.4/2.5	0	2+	0	0	1+	I*
35	52	M	0	0	0	+	+	0	+	0	1.4	3+	4.3	29	2.0	...	4.1/2.5	0	2+	0	+	3+	I
36	53	M	0	0	0	+	+	0	+	+	1.3	3+	...	20	2.0	...	3.0/2.3	0	4+	0	+	2+	I
37	46	M	0	0	0	+	+	0	+	+	0.1	3+	...	20	2.5	...	3.3/2.5	0	4+	0	0	2+	I
38	59	M	0	0	0	0	0	+	+	+	0.6	2+	...	20	3.2	170	3.9/3.2	0	4+	0	0	3+	I
39	50	F	0	0	0	+	+	0	0	+	0.3	1+	...	10	2.0	205/142	3.7/2.6	0	1+	0	0	3+	I
40	40	M	0	0	0	+	0	0	0	0	0.3	.....	...	10	....	...	4.5/3.8	1+	4+	0	+	2+	I
41	39	M	+	0	0	+	+	0	+	+	0.5	.....	5.8	20	10.0	196	2.5/2.9	0	2+	0	0	1+	I
42	56	M	+	0	0	+	+	+	+	+	0.3	1+	...	3	4.5	...	4.3/4.2	2+	4+	0	+	1+	I
43	51	M	0	0	0	+	+	0	+	+	0.5	1+	...	..	2.2	187	3.9/2.9	0	2+	0	0	2+	I
44	54	M	+	0	0	+	+	+	+	+	2.2	2+	...	40	9.2	...	3.9/4.7	1+	3+	0	0	1+	I
45	56	M	0	0	0	+	+	0	+	0	0.6	3+	...	27	4.7	...	3.4/3.3	0	3+	0	+	3+	I
46	41	M	+	0	0	+	+	+	+	+	2.8	3+	....	..	11.3	145/48	3.1/3.9	3+	3+	0	0	1+	I
47	53	M	0	0	0	+	+	+	+	+	1.0	4+	....	..	2.6	...	3.0/3.3	0	3+	0	+	1+	I

* See explanation in Table 1, page 302.

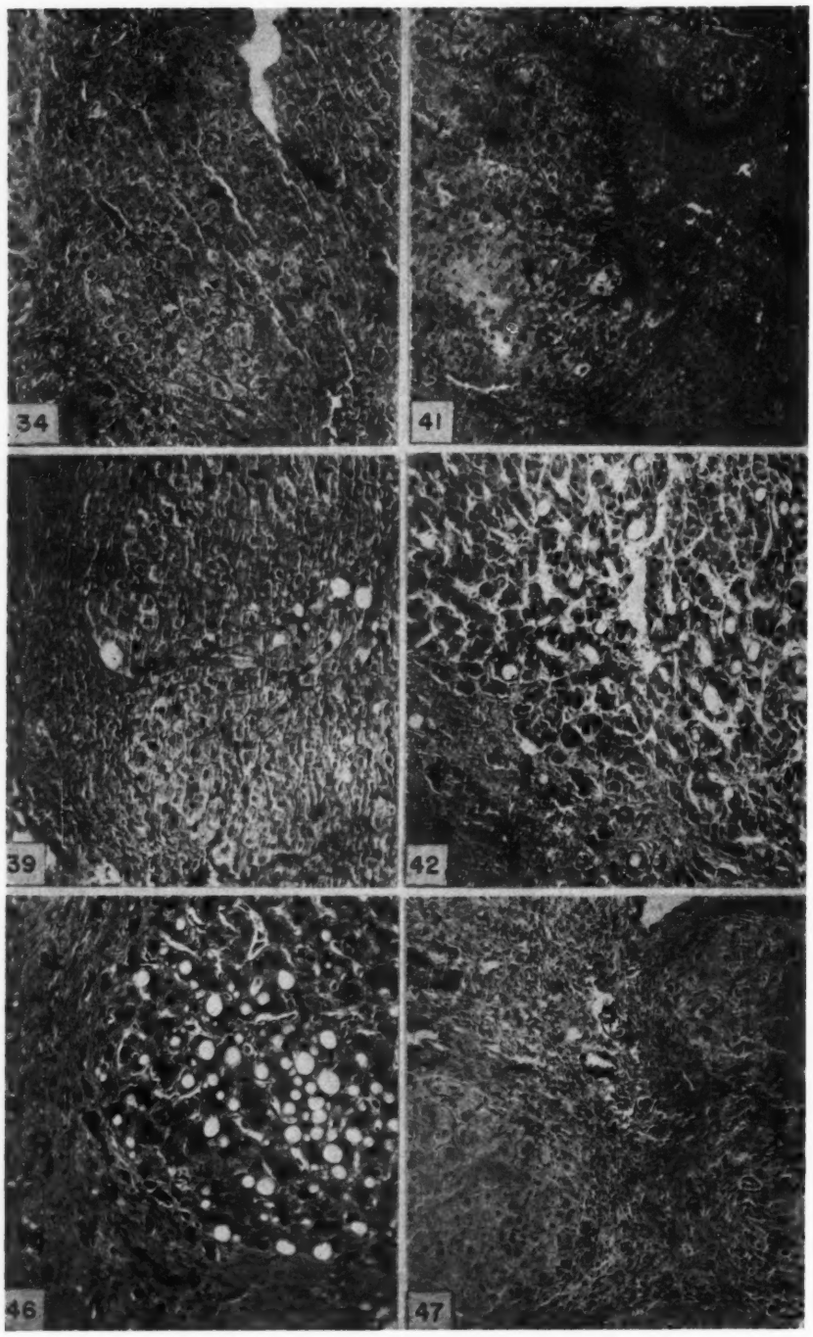

FIG. 3. Liver biopsies from six patients in Group III; "subsiding" hepatic insufficiency; hematoxylin and eosin stain, × 100.

patients in group II but the alterations in serum albumin and bilirubin were more marked.

The histologic lesions at postmortem are noted in Table IV and Figure 4. These sections showed wide variations in type and severity of lesions. In some patients fatty change was marked (Cases 51 and 52) resembling that noted in group I (Cases 9 and 12). In others fat was absent (Cases 49 and 53) and fibrosis and other changes were marked. Necrosis of liver cells was more frequently seen in this group than in any of the others. However, it was not present

in all patients in group IV. Neither necrosis nor any other lesion was unique to this group of patients.

In summarizing the data in group IV it appears that the clinical and "functional" changes seen in preterminal cirrhosis of the liver are similar to those seen in severe cirrhosis of the liver with ascites. Fatty changes may be prominent features of the histologic lesions. Necrosis of liver cells is seen more frequently and is more marked in this group of patients than in any other.

TABLE IV

GROUP IV

			Physical Signs								Laboratory Tests							Histology					
Case No.	Age	Sex	Jaundice	Edema	Ascites	Palpable Liver	Palpable Spleen	Vascular "Spiders"	"Liver Palms"	Cachexia	Bilirubin	Cephalin-Flocculation	Thymol Turbidity	BSP	Alkaline Phosphatase	Cholesterol/Ester	Albumin/Globulin	Fat	Fibrosis	Necrosis	Regeneration	Cellular Infiltration	Course
48	49	M	+	+	+	+	0	+	0	+	6.7	3+	....	35	2.0	...	*	3+	4+	2+	+	2+	D†
49	47	M	+	+	+	0	0	+	+	+	11.3	3+	....	45	...	...	1.7/4.0	0	4+	0	0	2+	D
50	51	M	+	+	+	0	0	+	0	+	2.3	3+	....	..	1.0	...	2.1/4.1	1+	4+	2+	+	2+	D
51	39	M	+	+	+	+	0	0	0	+	6.9	2+	....	..	2.5	...	4.1/4.3	4+	3+	1+	0	1+	D
52	57	M	+	+	+	+	0	+	+	+	7.0	4+	....	..	6.2	...	*	4+	2+	0	+	1+	D
52	51	M	+	+	+	0	0	+	+	0	19.9	4+	....	..	3.8	...	*	1+	4+	2+	+	3+	D
54	55	M	+	+	+	+	0	0	+	+	8.7	4+	....	..	5.0	...	2.9/4.6	2+	4+	2+	0	2+	D
55	60	M	0	+	+	+	+	+	+	0	0.7	4+	....	25	3.0	...	2.5/3.8	0	3+	1+	0	3+	D
56	59	M	+	+	0	+	0	+	+	0	2.5	3+	....	25	2.5	...	2.5/3.2	4+	3+	2+	+	2+	D
57	48	M	+	+	+	+	+	+	+	+	18.8	4+	....	..	2.0	...	2.7/4.7	0	2+	3+	+	4+	D
58	62	M	+	+	+	+	0	+	0	0	1.9	4+	23.0	..	3.6	...	2.0/4.1	3+	3+	3+	0	2+	D
59	48	F	+	+	+	+	+	+	0	0	14.0	4+	....	..	2.0	157/65	4.2/2.8	4+	3+	2+	0	1+	D
60	57	M	+	0	+	+	0	0	0	+	2.5	2+	....	..	...	...	2.2/3.4	0	4+	0	+	3+	D
61	59	M	+	+	+	+	+	+	0	0	18.0	.....	10.0	..	...	...	2.6/4.6	3+	3+	1+	+	2+	D
62	62	M	+	+	+	+	+	+	+	+	4.5	3+	6.1	..	4.2	98	*	3+	4+	1+	+	1+	D

* Receiving intravenous human albumin.

† See explanation in Table I, page 302.

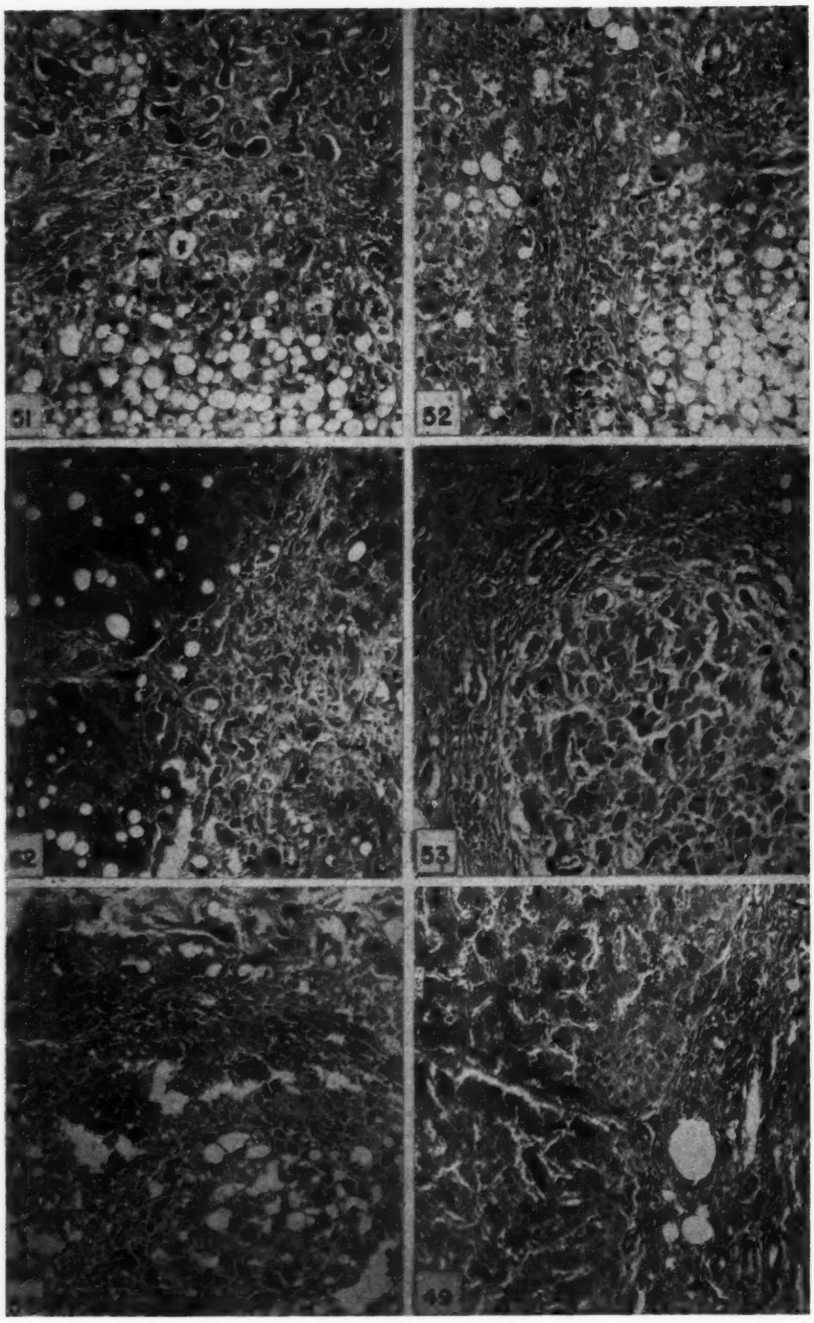

FIG. 4. Postmortem sections of liver from six patients in Group IV; death from hepatic insufficiency; hematoxylin and eosin stain, × 100.

The data do not shed any new light on the basic mechanisms involved in death from liver disease.[18]

COMMENT

Recently several papers have appeared in which attempts have been made to correlate abnormalities in liver function with structural changes in the liver.[7–10] These authors have considered many different types of liver diseases, including infectious hepatitis, coarsely nodular cirrhosis and biliary cirrhosis as well as Laennec's cirrhosis. The present report is concerned with what is presumed to be a relatively homogeneous group of alcoholic, inade-

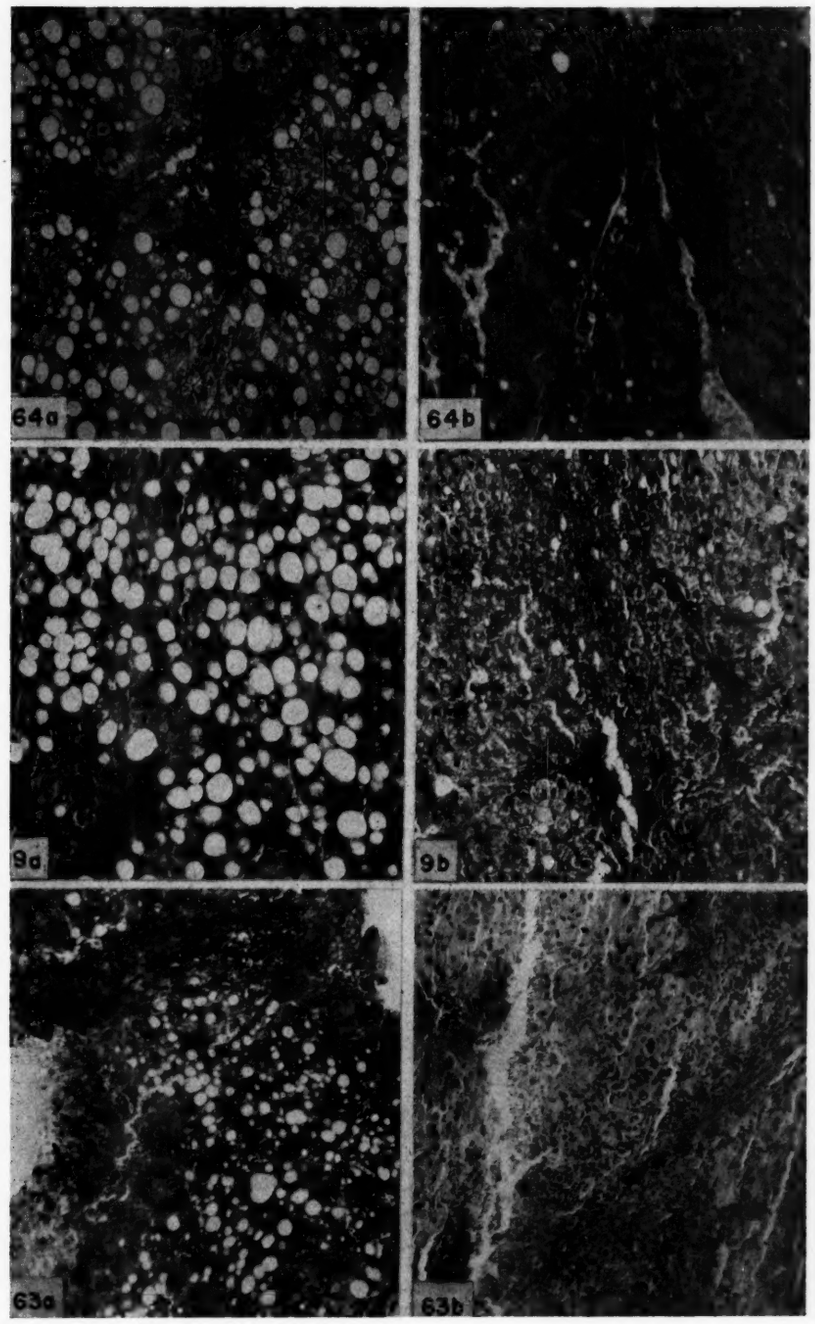

FIG. 5. Liver biopsies from three patients with fatty infiltration before and after 28 days of "regular" hospital diet; hematoxylin and eosin stain, × 100.

quately nourished patients with histologic liver lesions of the type associated with Laennec's cirrhosis. From the data presented it would appear that the severity of illness, as shown by the varying clinical states of the patients, was associated with varying degrees of abnormality in the liver function tests, especially in the levels of serum albumin and bilirubin. The most critically ill patients (groups II and IV) showed the most markedly abnormal laboratory data. The histologic lesions did not seem to be correlated with the clinical or "functional" states. Within any one group of patients considerable variation in severity of histologic lesions may be observed.

While there may be some general differences in the over-all histologic lesions when groups are compared, as in the amount of fatty infiltration in groups I and II, and of fibrosis in groups I and IV, for any particular patient no definite pattern was noted. The exception seemed the high incidence of liver cell necrosis found in group IV.

These data suggest that the functional integrity of the hepatic parenchyma is the critical factor in this disease. It may be that characteristic histologic changes, eventually to be demonstrated by special histochemical technics, are involved in alterations in cell functions. However, the conventional liver function tests and hematoxylin- and eosin-staining technic do not detect these relationships.

One histologic change which has received much attention is fatty infiltration of the liver. Several authors have shown this state to be reversible.[15,19,20,24] Figure 5 shows this phenomenon in three patients (Cases 9, 63 and 64) after an interval of twenty-eight days of regular hospital diet (P-75, C-250, F-75) without the addition of extra choline or methionine. During that time improvement occurred in the clinical states as well as in liver function tests. This phenomenon has been observed in seven other patients.[21] However, clinical and functional improvement may occur without disappearance of fat.[22] The lipotropic effect on the liver seems to be related to the level of protein intake.[22] While extradietary choline and methionine are not necessary for lipotropic effects to be manifest,[15,21,22,24] it is likely that the protein in the diet acts through the methionine-choline system. Proof for this concept is lacking in man.

Patek[12] has observed that "the evidence for histologic improvement associated with clinical improvement has been unimpressive, and there may be vast structural derangement for years after clinical improvement has occurred." In several patients with cirrhosis of the liver who improved clinically and functionally serial biopsies have shown little change except for disappearance of fat.[23] However, Volwiler et al. have stated "that under good dietary treatment the acute progressive histologic features of the hepatic parenchymal cell degeneration, even in a severely chronically diseased liver, may disappear within a few weeks."[15] More detailed study along these lines is needed.

It follows from the data presented that while the information obtained from the liver biopsy in Laennec's cirrhosis of the liver may be very valuable, interpretation with regard to prognosis and clinical course should be made in the light of complete study of the patient.

SUMMARY AND CONCLUSIONS

1. Sixty-two patients were studied in different clinical stages of Laennec's cirrhosis of the liver. They were investigated by the usual liver function tests and by needle biopsy of the liver.

2. No good correlation could be found between the clinical state and the histologic lesions or the measured "functional" state of the liver and the histologic lesions.

3. The clinical state and measured "functional" state seemed to be related.

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Weil's Disease*

Report of Five Cases

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LEPTOSPIRA icterohemorrhagiae infection in man (Weil's disease) has been recognized many times since 1922 when Wadsworth and his co-workers[1] reported its occurrence in one of their laboratory assistants. In March, 1948 a survey of the American literature by Molner, Meyer and Raskin[2] revealed a total of 228 cases of Weil's disease, to which they added sixty-five previously unreported cases from the Detroit area. The vast majority of these 293 cases have been reported since 1934, probably coincident with the description in that year by Schüffner[3] of the serum agglutination test employing cultures of leptospirae killed by and preserved in formalin. By using the agglutination test diagnosis is feasible after the tenth day of illness, and reliance for clinical diagnosis no longer rests on dark field examination of blood, a test of questioned reliability,[12] and on guinea pig inoculation, a procedure fraught with technical shortcomings.[14]

In this report we describe five more instances of human Lept. icterohemorrhagiae infection encountered during the past twelve years at the Beth Israel Hospital, New York. The diagnosis in the first case was not suspected during life but rests on postmortem findings. In the other four cases, as our experience with the disease increased, suspicion of the correct diagnosis led to early serum agglutination tests and corroboration of the diagnosis. The protocols of these five cases are herewith presented in their chronologic order.

CASE REPORTS

CASE 1. O. L., a thirty-eight year old married white female comptometer operator, became ill following a severe sunburn of the upper part of her body three months before admission to the hospital on October 17, 1936. Fever reaching a 104°F. maximum was present continuously in these three months. She remained in bed because of the skin blistering during the first five weeks of her illness. For six weeks prior to admission she had urinary urgency with occasional incontinence, dysuria, frequency and nocturia but no hematuria. At that same time she developed a painless, generalized glandular enlargement which lasted for two weeks. Four weeks prior to admission she began to have frequent, formed bowel movements (six per day) compared with her former habit of one per day. There was no acholia. Three weeks before admission her right ear became painful and discharged spontaneously, the discharge of pus persisting up to the time of admission. Her past history revealed regular menses till the onset of her present illness, since which time she had no periods.

The temperature was 102.4°F., with a pulse rate of 120 beats per minute and a respiratory rate of 30 per minute at the time of admission. She was jaundiced and appeared acutely ill. Thick pus discharged from the right eardrum. The sclerae were icteric. The throat and uvula were diffusely red. The neck was moderately rigid. A few small cervical and right axillary lymph nodes were palpable. Coarse rales were heard at both lung bases. The heart was normal. The abdomen was distended and the liver was tender and enlarged to 4 finger breadths below the costal margin in the mid-clavicular line. The spleen was not palpable. The dorsa of both feet and the dependent parts of both elbows were edematous.

The urine had a specific gravity of 1.011, 2 plus albumin, no bile or urobilin, 2 plus benzidine, rare granular casts and 10 to 15 red blood cells per high power microscopic field. The red blood cell count was 3,120,000 per cu.

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mm., the hemoglobin 76 per cent. The white blood cell count was 6,400 per cu. mm. with the following differential: 72 per cent segmented polymorphonuclears, 10 per cent staffs, 10 per cent lymphocytes and 8 per cent monocytes. Blood culture taken on the second day produced no growth. The following blood chemical examinations were made on the third day: icterus index 36.6; serum bilirubin 6.0 mg. per cent; serum proteins 3.6 Gm. per cent (albumin 1.9, globulin 1.7); glucose 86 mg. per cent; nonprotein nitrogen 85 mg. per cent; calcium 9.0 mg. per cent; phosphorus 11.7 mg. per cent. The stool was negative for bile but positive for blood. Bedside roentgenographic examination of the abdomen and chest revealed enormous enlargement of the liver shadow, with no elevation of the diaphragm, and areas of consolidation in the right upper, right lower and left lower lobes of the lungs.

Tentative diagnoses were sepsis, lupus erythematosus or liver abscess. Pneumonia was terminal. The patient became more deeply jaundiced and then irrational and somewhat stuporous. Her temperature remained between 102°F. and 104°F. She was treated supportively with a small transfusion and continuous slow intravenous fluids containing glucose and calcium. On the fourth hospital day she became increasingly irrational and mentally clouded, the pulse rate increased to 170 per minute and she died on the fifth day.

The necropsy report revealed that the hands were slightly edematous and that the lower extremities were pale and considerably edematous. The subcutaneous fat was edematous. The abdominal cavity contained about 700 cc. of light yellow, clear fluid. The peritoneum was smooth and glistening. The lower edge of the liver protruded from the costal arch for about 2 cm. The left lower lobe, the right upper lobe and the posterior thirds of the right middle and lower lobes of the lungs were diffusely firm and deep red with fine fibrinous layers on the corresponding pleural surfaces. These portions of the lung were firm and heavy, containing much blood and very little air. A few small areas were firmer and paler. Material scraped from the cut surfaces was deep red and glairy. The bronchial mucosa was deep red. The hilar lymph nodes were swollen, not calcific. Both kidneys peeled easily out of their capsules. The surfaces were smooth, hyperemic, jaundiced. The markings on the cut surfaces were normal. The liver was large (2,055 Gm.) pale yellowish-pink and firm, with normal acinar markings. The liver vessels were intact.

Microscopic examination of the lung revealed that the alveoli in the inflamed areas were filled with polymorphonuclear leukocytes. There was some fibrin. In some portions, mononuclear elements also were seen. Aside from occasional cocci, no micro-organisms were found. The pleura over the inflamed areas was covered with fibrin and leukocytes. The peripheral portions of the liver lobules contained much fat in large droplets. The central portions were almost free of fat. There was little fat in the Kupffer cells. There was no evidence of biliary stasis. The kidneys showed a picture of diffuse intra- and extracapillary glomerulonephritis. In the glomeruli the nuclei appeared numerous; there were small and larger fibrinoid necroses; in some the walls of the capillaries appeared swollen. The first portions of the convoluted tubules were wide. In many glomeruli, adhesions were seen between the two layers of Bowman's capsule. The tubules contained hyaline casts with varying degrees of biliary imbibition. There were a few compact bile casts. Few hemoglobin casts were seen. The tubular epithelium had severe cloudy swelling. In many cells the nuclei stained poorly; there seemed to be some signs of regeneration. Aside from the stasis and the casts the pyramids showed nothing remarkable. There was no interstitial inflammation. There was no old kidney lesion and the kidney vessels appeared normal. The fatty change was remarkably slight.

In the bloody material scraped from the cut surfaces of the pneumonic portions of the lungs spirochaetes were found in dark field examination which in morphology corresponded to the Lept. icterohemorrhagiae of Weil's disease. The material contained other micro-organisms. It was impossible to culture the spirochaete. The guinea pig inoculated died of mixed infection. The search for spirochaetes in other organs of the patient was fruitless.

Diagnosis: Weil's disease (?); pneumonia of left lower lobe, right upper lobe and posterior portions of right middle and lower lobes; diffuse intra- and extracapillary glomerulonephritis; fatty change in liver, hemangioma of liver; severe jaundice, anemia.

Comment. A thirty-eight year old woman was ill three months, the illness culminating

in a five-day hospitalization period and death. She was febrile, jaundiced and azotemic. At necropsy leptospirae were found in the lung.

CASE II. F. B., a forty-three year old seamstress, was well until she fainted in the bathroom while urinating five days before admission to the hospital on July 19, 1940. The day after fainting her temperature was 105°F. She repeatedly took powders prescribed by her physician and fainted within an hour after each dose. Three days before admission she developed pains in the back on a level with her epigastrium, followed by cramping and steady pains in both knees. Thereafter, epigastric pains set in, radiating to the back and right shoulder persisting until the day before admission. Nausea appeared and she vomited daily. Her appetite was poor and she complained of headache all week. For five days she had had no bowel movements. No jaundice was noted. She stated that four years ago her urine contained casts.

At the time of admission her temperature was 104.2°F., pulse rate 120 beats per minute, respiratory rate 40 per minute and blood pressure 130/78. She appeared acutely ill. Hair on head was sparse. The conjunctivae were diffusely injected. There was a suspicion of scleral icterus. The pharynx was red. A few rales were heard at the left basal lung field. Examination of the heart was negative. The liver and spleen were not palpable. There was no costovertebral tenderness. Deep palpation in the right lower abdomen elicited tenderness. A paronychia was found on the distal phalanx of the third finger of the right hand. Diagnostic impression on admission was toxic hepatitis or acute cholecystitis with cholangitis. On the day after admission icterus had increased sufficiently to be unquestioned.

Urine on admission had a specific gravity of 1.018, 2 plus albumin, frequent granular casts, 6 to 8 red blood cells and 10 to 12 white blood cells per high power microscopic field, no glucose, acetone, diacetic acid, bile or urobilin. The stool appeared clay-colored and was free of blood. The blood count was 4.37 million red blood cells per cu. mm., 82 per cent hemoglobin, 14,400 white blood cells per cu. mm., with a differential of 80 per cent polymorphonuclears, 10 per cent staffs, 6 per cent lymphocytes and 4 per cent monocytes. The sedimentation rate was 144 mm. in one hour. Blood chemistry tests on the second hospital day revealed non-protein nitrogen value of 54 mg. per cent, icterus index of 26.8 units, and a blood cholesterol of 168 mg. per cent, with 84 mg. per cent ester. The blood amylase was 97 units.

On the second hospital day almost complete anuria set in and continued for two days. The non-protein nitrogen value rose to 75 mg. per cent. The icterus index rose to 55. Despite the anuria, azotemia, jaundice and continued high temperature the patient remained alert and even comfortable. On the fourth hospital day she began to put out increasing volumes of urine, totaling 660 cc. on the fifth day and 1,720 cc. on the sixth day. The temperature reached normal on the sixth day and then rose to 103°F. on the seventh day. On this same day she manifested a diffuse maculopapular pink eruption with confluence of lesions, blanching on pressure. It was most noticeable on the extensor surfaces of the extremities and in the skin folds but spared the face. The diagnosis of Weil's disease was postulated at this time and was confirmed by the agglutination of the patient's serum, taken on the fifth hospital day, by Lept. icterohemorrhagiae up to a titer of 1:5,120.

The temperature remained irregularly elevated up to 103°F. during the second and third weeks, hovered between 99°F. and 101°F. in the fourth week and returned to normal gradually in the fifth week. In the second week anemia was evidenced, with 2.82 million red blood cells per cu. mm. and 60 per cent hemoglobin. The white blood cell count at this time was 38,000 per cu. mm. The non-protein nitrogen reached a height of 80 mg. per cent on the sixth hospital day. The icterus index reached a maximum of 104.8 on the eighth hospital day. The cholesterol total fell to 128 mg. per cent on the fourth hospital day. Esters were 62 mg. per cent. The skin eruption lasted about five to six days. Serum specimen of the eleventh day in the hospital revealed an agglutination titer of 1:10,000 against Lept. icterohemorrhagiae. Transfusion was given because of the anemia. Convalescence was uneventful except for a persisting pyuria due to chronic pyelonephritis and a fixation of specific gravity of the urine. She was discharged after eight weeks in the hospital.

Comment. This was a typical, severe case of Weil's disease in a forty-three year old

woman. She was febrile for four weeks, jaundiced and azotemic. Anuria existed for two days. Conjunctival injection was prominent. A maculopapular eruption of the skin was noted. Diagnosis was made by serum agglutination test. She was well after fifty-six days in the hospital except for a complicating pyelonephritis and persistent impairment of urinary concentration.

CASE III. P. C., a twenty-three year old white unmarried male florist, was admitted to the hospital on January 3, 1942, because of fever, malaise and cough of five days' duration. He was well until five days before admission when he felt marked malaise, nausea, weakness and headache, followed by shaking chills that night. His temperature ranged between 101°F. and 105°F. He developed a cough productive of thick, non-bloody sputum and accompanied by pain in the entire chest. During the five days of illness he had two easily controlled nosebleeds. There were several episodes of vomiting with constant anorexia. His bowels, previously reguar, became constipated. He worked in a basement floral shop where rats were seen.

On admission the temperature was 103°F., with a pulse rate of 108 beats per minute and a respiratory rate of 30 per minute. He appeared acutely distressed, with grunting respiration. He had a nasal discharge. The pharynx was injected. The lungs showed increased tactile fremitus over the right lower chest, with some dullness to percussion, diminished breath sounds and fine dry rales at the right base posteriorly. Remainder of the physical examination was negative. Impression on admission was that he had right lower lobe pneumonia.

On admission the urine had a specific gravity of 1.018, no albumin, no bile and occasional red blood cells and 2 to 3 white blood cells per high power microscopic field. The white blood cell count was 15,000 per cu. mm. with the following differential: 72 per cent polymorphonuclears, 12 per cent staffs and 14 per cent lymphocytes. Roentgenographic examination of the chest revealed no infiltration or consolidation of the lungs.

On the second hospital day he appeared jaundiced and his liver was tender and palpable 1½ finger breadths beneath the costal margin. The icterus index, which was elevated, reached its maximum value of 40 units on the fourth hospital day. The serum bilirubin level was 5.0 mg. per cent at this time. The fact that 10 Gm. sulfathiazole had been administered during the first two days of hospitalization led to the suspicion of toxic hepatitis but blood serum taken on the sixth hospital day agglutinated Lept. icterochemorrhagiae in a dilution of 1:320. Lept. canicola agglutination occurred in a titer of 1:640. Repeated tests on serum taken on the eighteenth hospital day revealed a titer of 1:10,000 against Lept. icterohemorrhagiae and 1:160 against Lept. canicola. At the patient's place of business, where rats were numerous, there was a police dog. Examination of the dog's urine was negative for leptospirae.

The jaundice decreased gradually over a three-week period. The temperature fell to normal on the sixth hospital day and then rose gradually to a maximum of 102°F. a week later. During the third and fourth weeks low level of fever persisted (up to 101°F.) and thereafter the temperature remained normal for the most part. The blood non-protein nitrogen value was never abnormal. The urine specific gravity was not impaired and albumin in the urine did not exceed a trace. Granular and hyaline casts and rare red blood cells were seen in the urine sediment at the height of the illness. The erythrocyte sedimentation rate was elevated during the first five weeks of hospitalization, generally paralleling the clinical picture, with a maximum of 45 mm. in forty-five minutes. During the fourth week of hospitalization the patient manifested large smooth areas of alopecia of the scalp. This loss of hair, occasional complaint of upper abdominal pain and several spontaneous epistaxes were the only untoward episodes in his gradual convalescence. He was discharged after fifty days of hospitalization.

Comment. A twenty-three year old male florist presented a respiratory illness with epistaxes. Fever persisted for three weeks. He became jaundiced. No azotemia developed but albuminuria and microscopic hematuria and casts were noted. Diagnosis was made by the serum agglutination test. An occupational contact with rats was elicited. Alopecia occurred during convalescence. He was well after fifty days in the hospital.

CASE IV. M. S., a fifty-eight year old white unmarried male plumber, entered the hospital on October 26, 1946, with a chief complaint of

fever of four days' duration. For four days he had experienced short shaking chills. At the onset he also noted a sudden onset of anorexia, malaise, frontal headache and insomnia. Three days before admission he felt pain in both legs with marked weakness. His work took him into various sewers and cellars inhabited by rats.

On admission his temperature was 105.8°F., pulse rate 128 beats per minute, respiratory rate 20 per minute. His blood pressure was 104/60. He appeared acutely ill, perspiring profusely. There was no jaundice. His skin was flushed but clear. The fundi showed moderate arterial tortuosity and some arterial-venous compression but normal discs. His throat was inflamed. The lungs were clear to percussion and auscultation. The heart revealed a questionable auricular fibrillation with an apical rate of 128 and a radial rate of 92 beats per minute. The liver was felt 1 finger breadth below the costal margin.

On admission the urine had a specific gravity of 1.014, a trace of albumin, 1 plus acetone, no glucose, a few granular casts, no red blood cells and occasional white blood cells. The white blood cell count was 13,200 per cu. mm., with 84 per cent polymorphonuclear cells, including 42 staff cells, 10 per cent lymphocytes and 6 per cent monocytes. The erythrocyte sedimentation rate was 92 mm. in one hour. The blood non-protein nitrogen on the third day was 93 mg. per cent. Roentgenogram of the chest showed no abnormality of the heart or lungs. Electrocardiogram (fifth day) showed a regular sinus rhythm and insufficient changes to indicate myocardial involvement.

Shortly after admission he was tentatively considered to have a respiratory infection. No specific antibiotics were administered. The temperature fell on the second day and remained between 98°F. and 101°F. for the subsequent four days. On the fifth day of hospitalization there was an icteric tint to the skin and sclerae, and the liver was tender and enlarged to 3 finger breadths below the costal margin. At this stage diagnosis of Weil's disease was suggested. On the sixth day the urine was positive for bile and urobilinogen. The icterus index was 34.2 units. The cephalin flocculation test was 3 plus in twenty-four hours, 4 plus in forty-eight hours. The non-protein nitrogen was now 200 mg. per cent, the carbon dioxide of the blood 23.5 volumes per cent, the total protein 3.7 Gm. with 1.2 Gm. of albumin and 2.5 Gm. of globulin. The jaundice was deepening. Bilateral conjunctivitis was noted. The fundi showed normal discs with congestion of the vessels.

On the seventh day the temperature rose to 102°F. and the patient was definitely weaker with clouded sensorium. The liver increased in size to the level of the umbilicus. No spirochaetes were seen on blood smear or in the urine; guinea pig inoculation was negative, but serum taken on the ninth day agglutinated Lept. icterohemorrhagiae in a dilution of 1:320 and Lept. canicola 1:40. Penicillin therapy was begun this day in dosage of 50,000 units intramuscularly every three hours. The temperature fell by lysis, reaching normal gradually by the fourteenth day and was essentially normal during the remainder of his five and one-half weeks of hospitalization. Penicillin was administered for ten days. On the sixteenth day the serum agglutination titer against Lept. icterohemorrhagiae had risen to 1:2,500 and against Lept. canicola to 1:160. The blood cholesterol in the second week was 137 mg. per cent with esters 65 mg. per cent. The total blood proteins at the end of the second week were 4.6 Gm. per cent, with albumin 1.3 Gm. and globulin 3.3 Gm. No albumin appeared in the urine after the fifteenth day. At no time were red cells found in the urine. After the nineteenth day hyaline casts were no longer seen in the urine. In the fourth week the icterus index was normal (8.8 units), the total blood proteins 5.9 Gm. per cent, with 3.5 Gm. albumin and 2.4 Gm. globulin. The alkaline phosphatase was 3.2 Bodansky units. The cephalin flocculation was 3 plus at forty-eight hours. Anemia was present, the hemoglobin being 64 per cent (10 Gm.) as compared with 94 per cent (14.5 Gm.) on admission.

During the height of illness in the second hospital week a generalized maculopapular eruption, particularly heavy on the trunk, was noted. It lasted about a week. On the nineteenth hospital day, when the jaundice was gone and the azotemia had almost disappeared (45 mg. per cent non-protein nitrogen), the patient suddenly developed blurring of the vision of the left eye. The eye consultant interpreted this to be due to an optic neuritis. There was blurring of the left disc margins and marked constriction of the visual field of this eye. This gradually improved by the time of discharge. At the time of discharge on the thirty-ninth day the blood chemistry values were normal (except

for the cephalin flocculation test) and the liver was still palpable, although non-tender, at 4 finger breadths beneath the costal margin.

Comment. This was a fairly typical instance of a severe case of Weil's disease in a fifty-eight year old plumber with an occupational exposure to rats. He received penicillin after the diagnosis had been established by the serum agglutination test. Pains in the calves occurred early. Conjunctivitis was severe. Jaundice appeared after the initial temporary subsidence in fever. There was chemical evidence of liver damage. Azotemia was marked. At the height of the illness he manifested a maculopapular eruption on the skin of the trunk. Left optic neuritis complicated early convalescence. He recovered after forty days in the hospital.

CASE V. R. L., a twenty-seven year old white male educational director, was well until six days before hospitalization on February 18, 1947, when he experienced a shaking chill, fever, anorexia and malaise. Except for the chill these symptoms persisted until three days before admission to the hospital when he noted that his urine was dark and his skin slightly yellow. He was nauseated throughout the six days, vomited once, felt no abdominal pain. When seen by a private physician three days before hospitalization, he had a temperature of 103°F., a slow pulse and a palpable spleen. The next day he was obviously jaundiced. The day preceding admission his liver was palpable 1 finger breadth below the costal margin and the icterus index was 52.7 units.

On admission his temperature was 99.4°F., pulse rate 68 beats per minute, blood pressure 120/85. He was well developed and well nourished, with jaundiced sclerae and skin. His pharynx was injected. The remainder of the physical findings were negative except for a tender liver palpable 2 finger breadths below the costal margin and a spleen palpable 1 finger breadth below the costal margin.

The urine had a specific gravity of 1.012 and a trace of albumin but was otherwise negative. The hemoglobin was 104 per cent (16 Gm.). The white blood cell count was 6200 per cu. mm. with 40 per cent polymorphonuclears, 1 per cent eosinophiles, 1 per cent staffs, 49 per cent lymphocytes and 9 per cent monocytes. The icterus index was 52.6 units on the fourth day in the hospital and the blood non-protein nitrogen value was 29 mg. per cent. On the third hospital day serum agglutinated Lept. icterohemorrhagiae in a dilution of 1:1,000 and Lept. canicola in a dilution of 1:100.

The patient ran an uneventful, afebrile course during his seventeen days in the hospital. The pulse was slow, varying between 60 and 72. On admission the diagnostic impression was infectious hepatitis with a possibility of infectious mononucleosis. Sheep cell agglutination titers were 1:7 when performed on the first and ninth days in the hospital. On the ninth day serum agglutinated Lept. icterohemorrhagiae in a dilution of 1:10,000 and Lept. canicola in a 1:1,000 dilution. The icterus index fell to 28.5 on the tenth day. Treatment was entirely non-specific. He was well at the time of discharge on the seventeenth day.

Comment. This represents a mild case of Weil's disease in a twenty-seven year old male. He was afebrile during his seventeen days of hospitalization. He was jaundiced. Both liver and spleen were palpably enlarged. There was no azotemia. A trace of albumin was the only urinary abnormality. Diagnosis was accomplished by the serum agglutination test.

CLINICAL FEATURES

The most detailed and complete presentation of the clinical picture of Weil's disease is contained in the review by Ashe, Pratt-Thomas and Kumpe,[4] from which we draw heavily for the following typical picture. It is convenient to divide the disease into three stages: The first, or septicemic, stage usually lasts five days. It includes the onset and all signs and symptoms up to and including the appearance of jaundice. The onset is sudden. Common symptoms are severe frontal headache, chilly sensations (rarely frank chills), prostration, aching of the calf muscles, anorexia, nausea, vomiting, painful abdominal muscles, cough, hiccough and bloody sputum. There may even be pneumonia. The temperature is high and the pulse relatively slow. A rash is uncommon at this stage. Herpes is unusual. The ocular conjunctivae are moderately injected. The pharynx may

be injected with the patient unaware of a sore throat. Usually there is no lymphadenopathy. Petechial hemorrhages may be present. A leukocytosis of 14,000 to 20,000 white blood cells per cu. mm. is the usual blood count. Urinary output may be scant with albuminuria or even a full nephritic picture. Azotemia, rapidly increasing, characterizes this stage and precedes the appearance of jaundice. On about the fifth or sixth day the temperature falls abruptly to near normal and jaundice appears. Despite this fall in temperature the patient appears in a worse condition. This heralds the onset of the second stage.

The second stage is the stage of jaundice. The European authors emphasize that not more than half of the patients become jaundiced. The non-jaundiced group has no second stage and goes directly into convalescence. Exceptions to this, apparently, are those patients with severe meningitis. The renal failure becomes more marked in the second stage and the hemorrhagic tendency is noticeable. The patient is exceedingly toxic and semicomatose. Pruritus is rare despite the deep jaundice. Appetite may be completely diminished. The temperature is elevated up to 101°F. There may be a hemorrhagic herpes labialis. The liver is characteristically enlarged and tender. The spleen is not usually palpable. Death, when it occurs, usually takes place between the ninth and sixteenth days. In the United States the mortality rate has averaged 30 per cent. In non-fatal cases the patient becomes more rational at the end of the second week and puts out increased volumes of urine. The azotemia and jaundice subside. At this time two complications may appear: iridocyclitis and optic neuritis.

The third stage is the convalescent stage. It begins insidiously in the latter part of the second week or in the third week. The patient becomes free of symptoms except for marked weakness. The convalescence varies from two to ten weeks. Relapse is liable to occur in the third, fourth and fifth weeks but is brief and not of serious consequence. Leptospiral vegetative endocarditis is the most severe complication which may go undiagnosed until later.

Review of our cases reveals that Cases II, III, IV and V more or less fit into this typical picture. They were all acute in onset and febrile. Three of these patients had chills. Two of them complained of pains in the calves or knees. Anorexia, nausea, vomiting, headache and malaise were prominent. In one patient oliguria was outstanding. During the period of hospitalization two of these four patients showed high non-protein nitrogen values, two were relatively normal. All showed albuminuria and only the fifth patient failed to show microscopic casts, red cells or white cells in the urinary sediment. All were jaundiced. Only the third patient manifested a hemorrhagic tendency, the bleeding arising from the nose. In three the white blood cell counts were high and there was anemia. Two showed severe conjunctivitis. In all four the liver was tender and in three the liver was palpably enlarged. The fourth patient showed marked hepatic dysfunction by chemical tests. These four patients recovered.

Among these four cases there were four clinical observations that are worthy of special note:

(1) Cases II and IV presented during their second weeks of hospitalization (both were admitted four to five days after onset of the illness) a maculopapular eruption sparing the face, most marked on the trunk in one instance and the extensor surface of the extremities in the other and fading in about five days. Macular and scarlatiniform eruptions have been noted during the second stage of Weil's disease in about 10 per cent of the cases.

(2) Case II developed a complicating pyelonephritis and, even at the time of discharge from the hospital, a persistent impairment of urinary concentrating ability.

(3) Case III manifested a severe alopecia of the scalp on the twenty-fifth day of hospitalization. This corresponded with the beginning of his convalescent stage. This patient was a twenty-three year old male.

This finding, to our knowledge, has been mentioned only once in the literature. Stiles, Goldstein and McCann[5] describe the case of a seventeen year old schoolboy with anicteric leptospiral nephritis, contracted when swimming in the Erie Barge Canal, who noted in his convalescence and later return to school that his hair was falling out excessively.

(4) Case IV developed a complicating left optic neuritis on his nineteenth hospital day, his twenty-third day of illness. This corresponded to the end of his second stage, just as he was entering convalescence. This optic neuritis subsided by the time of discharge. As just mentioned this is a common complication at this time.

Review of Case I reveals several atypical features. The illness apparently coincided in onset with a severe sunburn three months before admission to the hospital. Fever was continuous. For the six weeks before hospitalization she had generalized lymphadenopathy. She was incontinent of urine. Her white blood cell count was 6,400 per cu. mm. The azotemia and jaundice were typical. She died after five days in the hospital. Antemortem diagnostic impressions varied among sepsis, lupus erythematosus disseminatus and liver abscess. In this case the diagnosis of Weil's disease rests on the postmortem finding of spirochaetes from lung scrapings, which were morphologically similar to Lept. icterohemorrhagiae. Admittedly this is not a secure basis for the diagnosis. The spirochaetes were not recovered by postmortem culture; the inoculated guinea pig died of mixed infection. The pathologist could make no definite statement concerning the importance of this finding but did suggest that the diagnosis of leptospiral infection be considered. Following this suggestion, a review of the clinical data made the diagnosis a very likely one which could explain many of the findings. Further indirect support was derived from the postmortem findings: enlarged liver with fatty changes, pneumonia, diffuse extracapillary and intracapillary glomerulonephritis, cloudy swelling of the renal tubules and no evidence in substantiation of the other diagnostic possibilities.

MODE OF INFECTION

The vast majority of known cases result from contact with the excreta of rats. Most reported cases have been in persons whose occupations demanded working in wet places where rats are common: poultry workers,[2] fish handlers,[6,11] miners,[9] sewer workers,[10] tunnel diggers,[4] slaughter-house workers,[2] those who have been swimming in or have fallen into rat-infested waters[2,5] and those who live or work in rat-infested premises.[7,8] Among our five cases the occupation in two instances furnished the clue to the mode of infection. Case III was a florist who was employed in a basement shop where rats were frequently seen. Case IV was a plumber who worked in sewers and cellars inhabited by rats. In the other three cases no proof of contact with rats was obtained.

The diagnosis of Lept. icterohemorrhagiae infection takes on added importance in any one case because of the possible infection through unsanitary working contions. It has become increasingly recognized that this is an occupational hazard although not an occupational disease. In the United States in 1936 a fish worker in New York State was the first case of leptospiral infection in which compensation was awarded.[6] Since April 1, 1940, it has been included in the schedule of industrial diseases under the Workmen's Compensation Act in Scotland and Wales.[9]

LABORATORY DIAGNOSTIC PROCEDURES

Final diagnosis rests with the bacteriologist and serologist whose responsibility it is to identify the causative organism. In the first week of illness the spirochaetes are circulating in the blood stream and can be demonstrated by direct dark field examination or by injecting blood into a guinea pig and reproducing the disease. In the second week the organism disappears from the

blood and appears in the urine and can be demonstrated by guinea pig inoculation. In the latter part of the second week, and subsequently, diagnosis is possible by agglutination reactions. Mice protection tests are specific and diagnostic[15] and are especially useful when the agglutination titer is low enough to be controversial.

The serum agglutination test employing Schüffner's technic is the most widely employed method. It is dependable and relatively rapid, and by its use most of the recorded cases have been diagnosed. A titer of 1:300 is generally considered diagnostic and generally shows increase in the early titer if repeated in the third week. The specific antibodies remain in the blood for years, Packchanian and Tom[12] reporting their presence for periods varying from one year up to at least twenty years and seven months after recovery. This persistence of antibodies makes retrospective diagnosis possible.[16] In our Cases II, III, IV and V diagnosis was accomplished by serum agglutination tests, the respective initial agglutination titers being 1:5,120 on the tenth day of illness, 1:320 on the twenty-first day of illness, 1:320 on the 13th day of illness, 1:1,000 on the 9th day of illness. In each instance the agglutination titer rose when repeated several days later.

THERAPY

Until recent years the treatment of choice was the immune (convalescent) serum[4] but its effect was not striking and it had the great drawback of being difficult to obtain. With the availability of penicillin and its proven value against spirochaetes of relapsing fever and rat-bite fever experimentally in animals, it was inevitable that penicillin should be employed against Lept. icterohemorrhagiae. In guinea pigs Heilman and Herrell[17] reported dramatic therapeutic effects. Augustine, Weinman and McAllister[18] concluded from their experiments with guinea pigs that penicillin has a suppressive effect when given before the appearance of clinical manifestations but not a curative effect. Larson and Griffitts[19] compared the individual effect of penicillin and specific immune serum in experimental leptospirosis in young white mice and hamsters. Their results indicate little choice between them Both agents were fully effective when administered as late as forty-eight hours after infection had been induced in mice but at periods beyond this their value materially decreased. By the time jaundice had appeared among the animals the mortality was practically the same among treated as among untreated controls. Patterson[20] reported on observations in human cases of Weil's disease, three in whom convalescent whole blood transfusions were believed effective and six in whom penicillin was deemed effective. Bulmer[21] recorded experiences with penicillin treatment in sixteen cases of Weil's disease among British soldiers in Normandy. He used dosages of 40,000 units at three-hour intervals. No patient was treated in the pre-icteric stage. He and his co-workers concluded clinically, with no attempt at statistical approach, that penicillin appeared to effect a dramatic improvement within thirty-six hours and a reduction in the duration of fever and the number of relapses. In all these reports on the use of penicillin, except that of Bulmer, the dosages were small (e.g., 15,000 units every three hours) as compared with those presently employed. Recently, Heilman[22] studied the therapeutic effect of another antibiotic, aureomycin, in experimental leptospirosis icterohemorrhagiae in hamsters and found it relatively more effective than penicillin. No clinical studies with aureomycin in Weil's disease have yet appeared.

In our five cases one patient (Case IV) was treated with penicillin. He received 50,000 units intramuscularly every three hours, commencing with the ninth day of hospitalization (the thirteenth day of illness) and for ten days in all. His temperature fell by lysis to normal over a six-day period. It is impossible to assess its value in this case.

An interesting method of therapy was reported in 1947 by Williams[23] who employed high spinal anesthesia at the level of the seventh thoracic vertebra in a sixty-one year old male. This patient had been ill for eight days, drowsy, deeply jaundiced, secreting small quantities of urine and with a blood urea value of 321 mg. per cent. Following administration of the spinal anesthetic (16 cc. of nupercaine), diuresis began, blood urea fell rapidly and improvement was dramatic. The rationale was a suspected diversion of blood from the renal cortex by a vascular spasm which could be relaxed by paralysis of the sympathetic nerves. Support is lent to this hypothesis by the brilliant researches of Trueta and his group[24] who demonstrated in rabbits actual by-passing of the renal cortex circulation via the vasa recta system.

SUMMARY

1. Five cases of Weil's disease are presented, with postmortem findings in the one fatal case.

2. Diagnosis was accomplished by serum agglutination tests in four of the patients and by postmortem microscopic examination of lung scrapings in the fifth.

3. Unusual clinical features noted in one or more of the patients include maculopapular skin eruption, pyelonephritis, persistent impairment of urinary concentrating ability and severe alopecia. Optic neuritis complicated one case.

4. In two of the patients a clearcut contact with rats was indicated.

5. Penicillin treatment was employed in one patient.

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Jaundice during Methyl Testosterone Therapy

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JAUNDICE with distinctive features has been reported as occurring during the course of oral methyl testosterone administration.[1] At the time of this preliminary publication only tentative conclusions could be drawn as to the relationship between the steroid and the jaundice. First, hepatic manifestations were uncommon with a drug of such wide usage. Second, it was a possibility that the jaundice represented merely coincidental infectious hepatitis. Furthermore, it was not clear whether the steroid or the vehicle in which it was administered had caused the toxic effects. Finally, it was impossible in two of our cases to reproduce jaundice by resuming methyl testosterone therapy after the initial attack had subsided. Evidence has been gradually accumulated to indicate that methyl testosterone itself may cause jaundice. A review of the clinical features of the syndrome is presented herein.

Six patients have been seen from 1942 to date at the Presbyterian Hospital, two within the past six months. A summary of the case history of each is appended. Five of the patients are men and one is a woman. Ages range from seventeen to sixty-seven. Three are of Italian and two of South American origin; the sixth is a native American of Irish ancestry. A seventh case has come to our attention through Drs. Allen Kenyon and Charles Test who have kindly permitted us to incorporate their findings (Case VII.)

Route of Administration and Dosage of Methyl Testosterone. Five of the six patients at the Presbyterian Hospital received methyl testosterone pills (Schering) by mouth. The sixth was given methyl testosterone linguets (Ciba) sublingually. Dosage schedules are summarized in Table I and range from 10 mg. twice daily sublingually to 20 mg. four four times a day by mouth. The patient from Billings Hospital received 25 to 50 mg. orally daily.

History and Physical Examination. Five of the six patients in the Presbyterian Hospital series took the drug for from three to four months before toxic manifestations appeared; the sixth, the woman, took the drug for only eight days. (Table I.) The patient from Billings Hospital had received the medication four months before becoming jaundiced. Premonitory symptoms consisted of nausea, malaise and vague gastrointestinal symptoms which usually began about one to two weeks before jaundice was observed. The appearance of the disorder was unrelated to the season of the year. (Table I.) There was no history of preceding upper respiratory infection or of contact with cases of hepatitis. None had received blood or plasma transfusions or had been exposed to any known hepatotoxic agent. The basic disorders for which the methyl testosterone was exhibited are listed in Table I. The patient, J. G., with low platelets and purpura was given the drug in an empirical attempt to increase capillary resistance with the hormone.

The degree of jaundice was uniformly intense. The liver was palpable in four of the seven patients, was firm but not tender. The spleen was felt in one instance. Itching was notable in only one case.

Course. The duration of jaundice was protracted. An elevated serum bilirubin persisted for from three weeks to three months. Only one patient in the series showed evidence of severe hepatic dysfunc-

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tion. Recovery was ultimately complete and apparently without residual liver injury in the two patients available for long term follow-up.

Laboratory Findings. The essential laboratory findings are summarized in Table II.

The total serum protein values were normal as were the albumin-globulin partitions. The total fasting serum cholesterol was not remarkable although the esterified fraction was considerably reduced and the free fraction correspondingly increased in the

TABLE I

CLINICAL DATA IN SIX PATIENTS WITH METHYL TESTOSTERONE JAUNDICE

Name	Age	Sex	Date of Admission	Diagnosis	Type of Preparation of Methyl Testosterone	Daily Dose gm.	Duration of Therapy before Jaundice	Duration of Premonitory Symptoms (wk.)	Duration of Jaundice (wk.)	Second Course of Therapy
J. M.	67	M	9/23/42	Idiopathic purpura, cause undetermined	Oral	0.01 5 i.d.	4 mo.	2	5	Yes, no jaundice in 3 weeks
B. P.	17	M	7/27/43	Eunuchoidism	Oral	0.02 4 i.d.	3 mo.	1	12	None
M. N.	30	F	11/15/43	Cushing's syndrome	Oral	0.01 3 i.d.	8 da.	None	12	None
M. P.	35	M	7/19/46	Eunuchoidism	Oral	0.02 3 i.d.	4 mo.	4	3	Yes, no jaundice in next 4 yr. on the drug
L. W.	39	M	4/1/49	Psychogenic impotence	Sublingual	0.01 b.d.	4½ mo.	1⅓	9	None
F. T.	27	M	6/2/49	Simmonds' disease due to craniopharyngioma	Oral	0.02–0.03 3 i.d.	4 mo.	2	9	None
R. A.	15	M	4/13/49	Simmonds' disease due to craniopharyngioma	Oral	0.025 0.d.–b.d.	4 mo.	2–4	7–8	Yes, no jaundice during 3 weeks

In the early stages of the disorder the urine contained bile and the stools were generally clay-colored. Serum bilirubin at its maximum ranged from 5.1 to 29.0 mg. per cent. The cephalin-flocculation test was negative throughout except in one instance when a 1+ reaction was observed early in the course of the disease. Thymol turbidity in the three cases in which the test was done was also negative. Serum alkaline phosphatase ranged from 5.6 to 13.3 Bodansky units per 100 cc., showing slight elevation but not attaining levels usually seen in long-standing intra- or extrahepatic obstructive jaundice.

three cases thus tested before the beginning of the recovery period. Galactose tolerance was normal in one and slightly reduced in the second of the two cases in which this test was performed. The intravenous hippuric acid test done in two patients revealed low excretion in one instance and low normal in the other. The sedimentation rate was only slightly elevated at one hour. Complete blood count and blood Kline tests were normal.

Liver Biopsy. A needle biopsy of the liver was performed in two cases and was repeated during the course of illness in patient L. W. In all three biopsies the lesions were

confined to the central zones of the liver lobule.

In the first biopsy, from patient L. W., the bile canaliculi in the central zones were dilated and plugged with masses of bile pigment. A moderate amount of bile pigment had accumulated in some of the liver cells. Minimal liver-cell damage was seen in the central zones. A small proportion of the cells revealed shrinkage, homogeneous acidophilic cytoplasm, pycnosis and multiplication of the nuclei. There was no inflammatory reaction in the liver lobule or portal areas or alteration in the normal configuration of the liver lobule. The bile ducts were not dilated and contained no bile.

A second biopsy from this patient taken later in the course of the disease revealed similar plugging of dilated canaliculi and more bile pigment within the liver cells. Only an occasional liver cell was necrotic; there was mild fat accumulation in some of the others. In some of the lobules connective tissue extended along the sinusoids in the central zones and in a few a small number of lymphocytes infiltrated the area.

A single biopsy done in the second case, patient F. T., revealed dilation and plugging of the bile canaliculi in the central zones as in the preceding biopsy. The liver cells were histologically normal with the exception of multiple nuclei in a few. There was no inflammatory reaction and the structures of the portal areas were normal.

Special staining technics for alkaline phosphatase in both biopsy specimens revealed a moderate degree of phosphatase activity in the sinusoid lining cells of the central zones and in the bile plugs filling the canaliculi. This is consistent with bile stasis limited to the bile canaliculi. More pathologic material is desirable to confirm this observation.

Thus the histologic lesion is that of a stasis of bile with plugging of the bile canaliculi in the central zones of the liver lobules and of very mild hepatic cell damage in these areas. There is no evidence of obstruction of the biliary system distal to the central zones.

CASE REPORTS

CASE I. U. H., No. 669062. J. M., a sixty-seven year old male, was first admitted February 9, 1942, complaining of purpura of two months' duration. His family and personal history were irrelevant. The patient had had malaria fifty years before admission, pneumonia fifteen years before and an appendectomy twenty-two years before. System review was negative. The present illness began suddenly with bleeding gums and purpura. There was no history of chemicals, drugs, infections, etc. Physical examination was essentially negative except for purpura of skin and mucosa, with the liver and spleen not palpable. Laboratory examination showed platelets 9,000 and chronically infected left mastoid cells, right frontal and both maxillary sinuses; it was non-revealing otherwise. The diagnosis was thrombopenia, cause undetermined. In June, 1942, it was decided to administer methyl testosterone in an attempt to increase capillary resistance or to stimulate bone-marrow production of platelets. The patient was given 10 mg. five times daily for two months and then 10 mg. three times daily for one month. At the end of this time he returned complaining of lethargy, nausea and vomiting for two weeks and dark urine and light stools for four days. The patient was readmitted. On physical examination during this second admission the liver was questionably palpable and the spleen was not felt. The rest of the examination was unchanged from the first admission except for the absence of purpuric manifestations. The essential laboratory findings are summarized in Tables II and III. Platelets on this admission were 74,000. The patient began to clear his jaundice after two weeks in the hospital. A retrial with methyl testosterone two months later, with 0.01 gm. daily followed by 0.01 gm. three times a day, failed to cause jaundice again during a three-week period. The patient was then lost to follow-up.

CASE II. U. H., No. 716331. B. P., a seventeen year old male, was admitted July 27, 1943, complaining of one week of anorexia and one day of jaundice. Family and personal history were irrelevant except that the patient had come to the United States six months before from his native land, Peru, to seek treatment for eunuchoidism. Previous health was irrelevant except for sporadic, inadequate, short bouts of testosterone propionate therapy for eunuchoidism. The present illness began three months

after the patient had been placed on methyl testosterone, 0.02 gm. four times daily, for his gonadal failure. Physical examination was negative except for the evident jaundice and a spleen palpable at the costal margin. The liver was impalpable. The essential laboratory findings have been summarized in Tables II and III. Improvement started in the fourth hospital week but was not complete until the twelfth week. The patient then returned to Peru.

CASE III. U. H., No. 725954. M. N., a thirty year old female, was first admitted November 15, 1943, for a work-up for Cushing's syndrome. The family history was negative except for diabetes in the father. Her personal history and previous health were non-contributory. The

TABLE II

LABORATORY DATA IN SIX PATIENTS WITH METHYL TESTOSTERONE JAUNDICE

Name	Urine Bile	Stool Bile	Cephalin-flocculation	Thymol Turbidity	Highest Serum Alkaline Phosphatase B.U.*	Serum Protein			Serum Cholesterol			Highest Serum Bilirubin mg. Per cent	Liver Biopsy
						Total gm. Per cent	Albumin gm. Per cent	Globulin gm. Per cent	Total mg. Per cent	Free mg. Per cent	Ester mg. Per cent		
J. M.	++	++	+, ±	−	8.3	7.1	4.4	2.7	−	−	−	9.5	−
B. P.	++++	0	neg.	−	12.2	6.2	4.2	2.0	141	85	56	29.0	−
M. N.	++	++	neg.	−	5.6	6.3	4.9	1.4	250	−	−	7.9	−
M. P.	+	0	neg.	−	9.5	6.3	4.4	1.9	286	−	−	5.1	−
L. W.	++++	0	neg.	neg.	11.1	6.4	4.0	2.4	257	128	129	17.1	+, +
F. T.	++++	0	neg.	neg.	13.3	6.9	4.5	2.4	279	206	73	21.0	+
R. A.	Pos.	+	neg.	neg.	17.6†	7.8	4.9	2.9	173	70	103‡	6.9	−

* Bodansky Units, normal: 1–4 B.U.
† King-Armstrong Units, normal: 4–12 K.A. units
‡ During recovery period

TABLE III

MISCELLANEOUS LABORATORY DATA IN SIX PATIENTS WITH METHYL TESTOSTERONE JAUNDICE

Name	Urine Urobilinogen	Serum Amylase K and M Units	Initial Prothombin Time Seconds	I.V. Hippuric Acid Excretion gm.	Galactose Removal Constant	Bromsulfalein Retention at 30 min.	Duodenal Drainage	Sheep-cell Agglutinin	X-rays
J. M.	....	..	....	...	...	.....	.....	...	Flat plate abdomen negative
B. P.	....	..	15.3	0.5	...	.....	Pancreatic enzyme function test normal	...	G.B., G.I. series negative
M. N.	....	..	10.6	1.1*					
M. P.									
L. W.	neg.	34	15.3	...	5.4†	80 per cent	A and B bile present; micr. negative	...	X-rays chest and flat plate abdomen negative
F. T.	neg.	..	15.4	...	4.1†	.....	.....	1:8	Flat plate abdomen negative
R. A.	1:40								

* Normal > 1.0 gm.
† Normal 4.2–9.5

present illness began with amenorrhea four years previously and had been progressively downhill. On physical examination there were "buffalo obesity" and atrophy of breasts and genitals but a blood pressure of only 128/90 and no unusual striae distensae. In the laboratory the essential findings were hemoglobin 13.5 gm. with total red blood cells of 6.6 million per cu. mm., calculated sodium of 139.8 mEq., blood calcium 10.3 mg. per cent, phosphorus 2.7 mg. per cent, alkaline phosphatase 6.3 Bodansky units per cent, cholesterol 330 mg. per cent and serum bilirubin 1.0 mg. per cent. X-rays of thoracic and lumbar spine revealed marked demineralization. Airograms of the adrenals showed an enlarged right adrenal. Oral glucose tolerance showed values fasting 92 mg. per cent; one-half hour 123, one hour 187, two hours 205 and three hours 224. Urinary total neutral 17-ketosteroids 6.1 mg. per twenty-four hours. One month after admission the patient was started on methyl testosterone, 0.01 gm. three times daily. Eight days later jaundice was noted. Physical examination was unchanged with liver and spleen not palpable. The essential laboratory findings relating to the jaundice are summarized in Tables II and III. The liver edge became palpable shortly after admission 2 cm. down. In the third week of jaundice an adrenal cortical adenoma was removed from the right adrenal, with progressive recovery from the Cushing's syndrome. Jaundice cleared three months after onset and menstruation started spontaneously two months later. The patient has been well to date.

CASE IV. U. H., No. 823426. M. P., a thirty-five year old male, was first seen April 9, 1946, when a diagnosis of uncomplicated eunuchoidism was made. Family and personal histories were irrelevant. The patient was born in Italy and had been in the United States since nine years of age. Previous health was non-contributory except for mumps at the age of four. The present illness consisted of a story of failure to mature. Unsuccessful therapy had been given with antuitrins for a year at the age of nineteen, with testosterone propionate for six months one year after this and again for brief periods when he was twenty-seven and thirty-two. The patient was married nine years before admission and consulted his local physician after five years of sterility. Azoospermia was found and for the past four years until six months before admission the patient was given methyl testosterone, 0.01 gm. daily. No therapy had been taken during the past six months. On physical examination the patient showed moderate obesity, female contour to hips, scant pubic hair with little face hair, a small penis and testes about 0.8 x 0.5 cm. The prostate was barely palpable. The rest of the examination was negative. In the laboratory the significant results were basal metabolic rate −18, fasting cholesterol 205 mg. per cent and the persistence of open epiphyses of the iliac crest shown by x-rays of the pelvis, indicating a bone age of less than twenty-five years. The patient was started on methyl testosterone by mouth, 0.02 gm. three times daily, March 19, 1946. After three months nausea was noted, followed after one month by gas, belching, anorexia and jaundice. The physical examination was unchanged except for the jaundice and marked increase in secondary sex character development. The main laboratory findings are summarized in Tables II and III. The jaundice cleared after three weeks. The patient was restarted on methyl testosterone two months later (0.02 gm. three times daily) and has remained free of jaundice to the present while still on the drug.

CASE V. U. H., 946649. L. W., a thirty-nine year old male, was first admitted April 1, 1949, because of jaundice for ten days. The family and personal history were irrelevant. His previous health was non-contributory except for psoriasis since childhood. The present illness began with the prescription of sublingual linguets of methyl testosterone, 0.01 gm. twice a day, in October 1948, for the treatment of impotency of six months' duration. About four and a half months later, three weeks before admission, "indigestion" and diarrhea were noted followed one week later by jaundice with grey stools and dark urine. The physical examination, apart from jaundice and a palpable liver 4 cm. below the costal margin, was negative. The main laboratory findings appear in Tables II and III. After three and a half weeks without clearing of the jaundice the patient was transferred to the Veterans Administration Hospital, Kingsbridge Division, and slowly improved over the next four weeks. Needle biopsy of the liver was obtained at the Presbyterian Hospital and again at the Veterans Administration. The patient is well at the present time.

CASE VI. U. H., No. 940324. F. T., a twenty-seven year old male, was first admitted to the Presbyterian Hospital June 2, 1949, complain-

ing of jaundice of two weeks' duration. The family history and personal history were noncontributory. Previous health was irrelevant. The present illness began in 1939 when a tumor of Rathke's pouch, an adamantinoma, was removed at the Neurological Institute. This was followed by x-ray therapy, a second partial removal of the growth in 1942, sudden permanent blindness in 1943 and classical Simmonds' disease, February, 1949. At this time desoxycorticosterone acetate, 0.005 gm. intramuscularly once daily, thyroid, 0.03 gm. once daily, and methyl testosterone, 0.01 gm. three times a day, postoperatively, were started. One month before admission the dose of the methyl testosterone was increased to 0.02 gm. three times daily. Itching, anorexia and drowsiness appeared two weeks before admission. On physical examination the patient was found to be icteric and totally blind with optic atrophy; he had a questionable liver edge 4 cm. below the costal margin, atrophic testes and scant pubic and axillary hair. The rest of the examination was irrelevant and the spleen was not felt. The laboratory findings are summarized in Tables II and III. The patient became drowsy and irrational for one week during the second to third week in the hospital but recovered with slow clearing of the jaundice beginning in the fourth to fifth week and completing at the ninth week after onset. During the last four weeks of his course the serum sodium which had averaged about 125 mEq./L. was only slowly restored to normal with salt and desoxycorticosterone.

CASE VII. R. A., a fifteen year old male, was first admitted to the Billings Hospital, Chicago, Illinois, September 24, 1948, complaining of headache for nine months. A suprasellar cyst, thought to be probably a craniopharyngioma, was demonstrated. A diagnosis of secondary hypopituitarism was made after extensive workup. The patient was given x-ray therapy. He was started on methyl testosterone, 25 mg. once daily, from November 12, 1948, to February 8, 1949; this was raised to 50 mg. daily from February 9 to March 31, 1949. From February 22 to February 28, 1949, the patient was readmitted to the Billings Hospital for undiagnosed fever clearing despite continued methyl testosterone therapy. Sodium chloride, 3 to 6 gm. daily, was also instituted. On April 13, 1949, the patient was admitted a third time because of jaundice for five weeks with light stools and dark urine. There was no recurrence of fever. On physical examination the only significant changes from the previous admissions were the evident jaundice and a palpable liver 2 cm. below the costal margin. The laboratory report was as follows: hemoglobin, 10.0 gm.; red blood count, 3.4 million; white blood count, 2,800; polymorphonuclears, 34 per cent; lymphocytes, 58 per cent; mononuclears, 3 per cent and eosinophiles, 5 per cent. Sedimentation rate was 16 mm. at one hour (corr.). The main findings are summarized in Tables I, II and III. The bilirubin fell progressively from shortly before admission to the point of clearing eight weeks after onset of jaundice. Methyl testosterone was recommended June 22 to July 18, 1949, 25 mg. daily, with no recurrence of jaundice.

CONCLUSION

The clinical features of jaundice following the administration of methyl testosterone have been described. The uniformity of laboratory findings and the details of the histologic picture indicate a characteristic type of hepatic injury. The outstanding disturbance is apparently a stasis and an accumulation of bile within the bile capillaries of the central portion of the lobule, with no evidence of obstruction in the larger bile ducts. The phenomenon is associated with a derangement of contiguous hepatic cells which, despite minor histologic alterations, remain viable and do not invoke a positive cephalin-flocculation reaction. Various metabolic activities of the hepatic cells, especially the function of maintenance of the cholesterol:cholesterol ester ratio in the serum, may show moderate impairment but the most striking functional disturbance is the failure to maintain the excretion of bilirubin and the flow of bile through the terminal biliary radicles. The cause of the bile stasis has not been determined with certainty. The absence of lesions in the portal triads or swelling of the bile ducts differentiates the jaundice following testosterone from the intrahepatic cholangiolitic obstructive jaundice which has been described following administration of arsphenamine and other drugs.[2] No coagulable fibrin-like matrix could be demonstrated in the bile plugs to explain their formation.

It is not improbable that injury to the hepatic cells by the drug leads to a disturbance of the normal hydration of the bile which becomes too viscous to flow through the intralobular duct system.

It is noteworthy that the hepatic lesion found in methyl testosterone intoxication gives rise to a clinical picture in which jaundice of conspicuous intensity occurs without the characteristic features of either severe parenchymal damage usually marked by a positive cephalin-flocculation reaction and striking disturbances of metabolic function or of biliary obstruction such as a definite elevation of alkaline phosphatase and of total cholesterol in the serum.

The evidence that methyl testosterone is the causative agent for the disorder is indirect. Intercurrent infectious hepatitis seems ruled out on both clinical and histologic grounds. Rarely cases of hepatitis are encountered which show chemical features similar to those described herein. However, inflammatory changes are usually demonstrable in the liver. The vehicles for the steroid have not been the same in all instances, are innocuous and would therefore seem of little etiologic significance.

The mechanism by which the toxic effects are produced is not clear. It seems improbable that methyl testosterone is a markedly hepatotoxic agent since the syndrome herein reported is rare despite widespread usage of the hormone. A drug sensitization or a personal idiosyncrasy might be assumed but this possibility must be accepted with caution in view of the failure of the two patients retreated at the Presbyterian Hospital to redevelop jaundice when the drug was resumed. Overdosage with the hormone also seems unlikely since as little as 20 mg. a day was sufficient to produce the difficulty in one instance.

SUMMARY

1. A syndrome of jaundice with distinctive features is described in association with methyl testosterone therapy. Seven cases are reported.

2. The laboratory findings are characterized by a negative cephalin-flocculation reaction, only moderately elevated serum alkaline phosphatase and a markedly increased serum bilirubin.

3. Liver biopsy suggests stasis of bile in the bile canaliculi and mild derangement of the contiguous cells.

4. The role of methyl testosterone as the etiologic agent is discussed.

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Osseous Gaucher's Disease*

Report of Two Cases in Siblings

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ALTHOUGH the occurrence of osseous lesions in Gaucher's disease is common, studies on such cases in siblings have not often been reported. For this reason and because in one case the roentgenogram was so bizarre as to present a diagnostic problem, two cases of the osseous form of Gaucher's disease in siblings are herewith presented, with a brief review of the pertinent literature.

CASE REPORTS

CASE 1. P. S. (N.H.H. No. C5884), a fifty-one year old housewife, entered the New Haven Hospital on January 3, 1948, because routine examination by a private physician had revealed splenomegaly and leukopenia. On admission the patient was asymptomatic. She had noted ease of bruising and of epistaxis for many years, the latter requiring frequent cauterization. Friends had long commented on the sallowness of her complexion. The medical history was non-contributory except for (1) an anemia known to have been present since before menarche, unresponsive to many courses of liver and iron therapy, (2) a single mild attack of cholecystitis in 1938, without jaundice or subsequent fatty food intolerance and (3) an attack of red, swollen, painful knee joints in 1928, with mild recurrence until 1940. The family history revealed only a high incidence of carcinoma.

Physical examination revealed a well developed, well nourished woman with pale mucous membranes, whose skin was ochre-colored, most marked in the malar regions. Pingueculae of the conjunctivae were noted bilaterally. A firm, non-tender spleen extended 2 cm. below the level of the umbilicus on inspiration. The liver edge was barely palpable at the height of inspiration, and a slightly tender, movable, round mass in the right upper quadrant was thought to be the gallbladder. There was no lymphadenopathy. A painless, non-tender enlargement of the distal third of the left femur was noted, and there were ecchymoses scattered over the legs. Other findings were not remarkable.

The patient's temperature, respirations, pulse and blood pressure during hospitalization were within normal limits. Laboratory examinations revealed an anemia which ranged from 3 to 3.5 million red blood cells, with 9.5 to 10.5 gm. of hemoglobin. Blood indices were normal, and reticulocytes were 0.8 per cent. The red blood cells were markedly macro-, aniso- and poikilocytotic with marked polychromatophilia. The white blood cell count ranged from 1,500 to 4,200; the differential count was normal. Blood Mazzini, urine and stool examinations were negative, and corrected sedimentation rate was normal. Platelets ranged from 82,000 to 164,000 by the Rees-Ecker method (normal: 250,000 to 500,000). The patient developed numerous petechiae below the site of application of tourniquet for venipuncture. Bleeding time, clotting time and prothrombin time were normal. Liver function tests were normal except for a 3+ cephalin-flocculation test. Vertebral marrow aspiration revealed a normoblastic hyperplasia as well as small numbers of typical Gaucher cells. (Fig. 1.) Roentgen studies revealed a non-functioning gallbladder without evidence of calculi. Films of the long bones revealed changes compatible with Gaucher's disease in the femurs (Fig. 2A), humeri, left carpal navicular, and phalanges of the hands (Fig. 2B); in addition, an atypical lesion in the distal left femur was noted. (Fig. 2C.) Films of the chest, skull, vertebrae and pelvis were normal. Blood chemical examinations were as follows (all within normal limits

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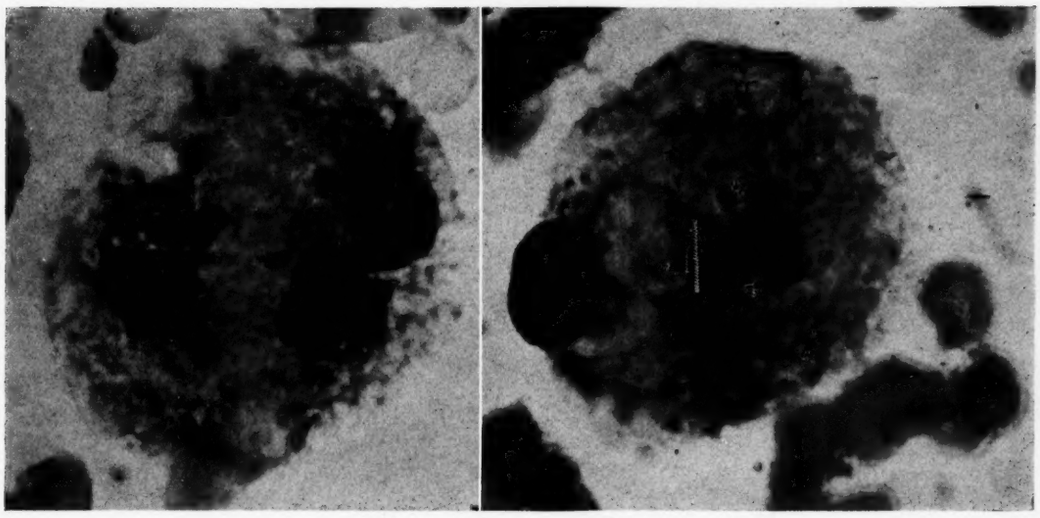
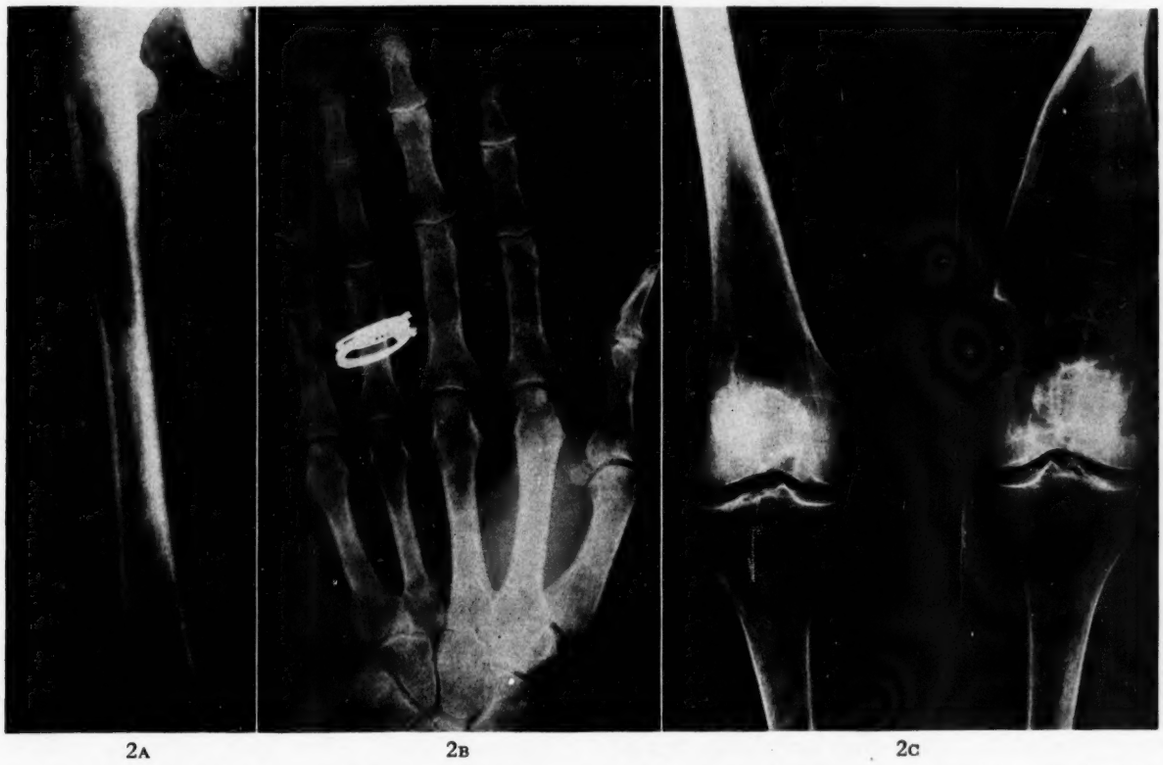


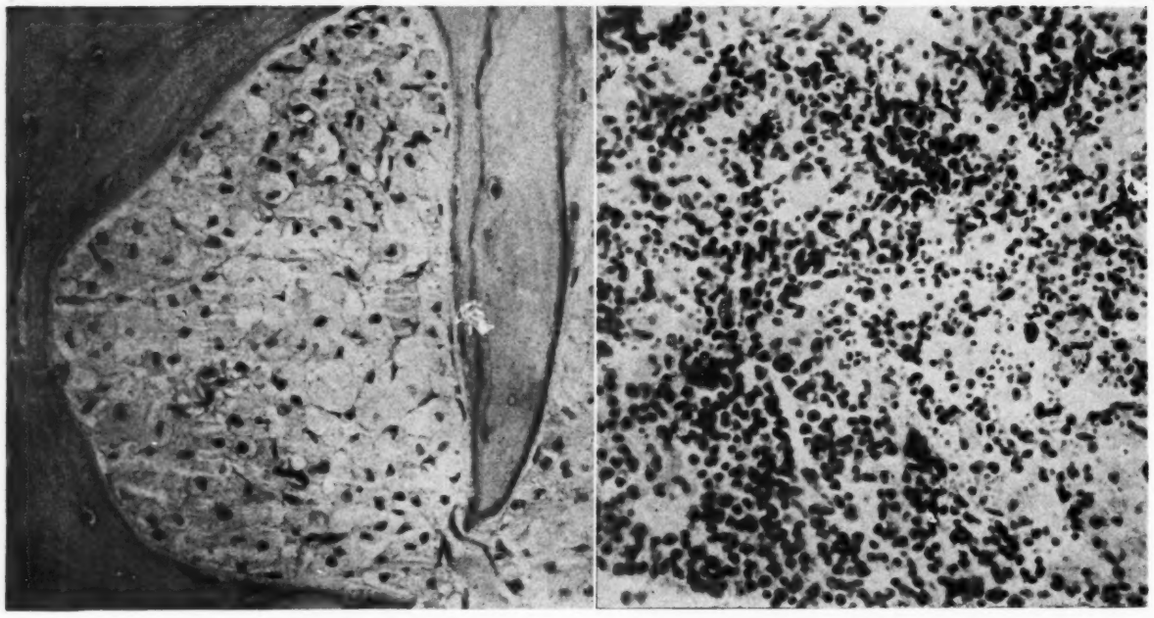
1A 1B

FIG. 1. A and B, two examples of typical swollen reticulum cells (Gaucher cells) from the vertebral bone marrow of patient P. S. The numerous cytoplasmic wavy fibrillae are not demonstrated by fat stains since the Gaucher substance is chemically inert. The single or multiple nuclei are small and eccentrically placed. These cells are characteristically 20 to 80 micra in diameter; compare in size with the neighboring erythrocytes. Wright-Giemsa stain, × 4400.



2A 2B 2C

FIG. 2. Roentgenograms of patient P. S. A, right femur; there is irregular thinning of the cortex characterized by endosteal scalloping, being particularly marked in the upper third of the diaphysis. B, left hand; changes in the short tubular bones similar to the changes noted in the femur are the result of endosteal absorbtion and irregular widening of the medullary cavity, particularly marked in the proximal phalanges of the second and third digits. C, comparison of distal thirds of both femurs. Evidence of club-shaped deformity on the left as the result of expansion of the bone and thinning of the cortex with an irregular trabecular pattern are somewhat suggestive of changes seen in giant-cell tumor of bone. The latter diagnosis was seriously entertained by a number of consultants prior to biopsy.



3A 3B

FIG. 3. A and B, biopsy specimens from lesion of the left femur shown in Figure 2C. Note the bone spicules in contiguity with fairly compact collections of Gaucher cells. The cells are polyhedral, rounded or oval-shaped, with small nuclei and much pale, finely granular cytoplasm. Hematoxylin and eosin stain, × 350.

by methods in use at this Clinic): non-protein nitrogen, 27 mg. per cent; fasting blood sugar, 91 mg. per cent; serum albumin, 3.7 gm. per cent; serum globulin, 2.4 gm. per cent; serum calcium, 10.4 mg. per cent; serum inorganic phosphorus, 3.7 mg. per cent; alkaline phosphatase, 10.0 King and Armstrong units. Serum lipid determinations were within normal limits, including free and total cholesterol, lipid phosphorus and serum fatty acids. After an uneventful hospitalization the patient was discharged on January 18, 1948, with a diagnosis of Gaucher's disease and chronic cholecystitis.

Because of the possibility that the bizarre lesion in the distal left femur was a giant-cell tumor, the patient entered the Hospital for Special Surgery, in New York City in April, 1948, for a biopsy. Photomicrographs of the biopsy specimen are shown in Figure 3;* these show the picture of Gaucher's disease without evidence of giant-cell tumor.

The patient is at present asymptomatic save for occasional epistaxis. Her two sons, aged twenty-two and twenty-five, have had complete skeletal films which are normal.

CASE II.† M. A., a male born in 1889, is the brother of the patient P. S. in Case I. In 1936 glycosuria led to the diagnosis of diabetes mellitus; he has been maintained to the present on controlled diet plus varying combinations of regular and protamine zinc insulin. An incidental finding in 1936 was a liver palpable 4 cm. below the right costal margin in the midclavicular line, and a spleen palpable 8 cm. below the left costal margin. Laboratory findings were hemoglobin 75 per cent, red blood cells 3.8 million, white blood cells 3,100, icteric index 9. On separate occasions in 1938 the patient fractured four ribs and the surgical neck of the left humerus, each after exertion or very mild trauma. Films revealed "some type of cystic bone disease," and the patient was treated with very large doses of vitamin D, without event. General health continued good but in 1941 the patient complained of pain in both arms. Roentgenograms indicated increased density in the vertebral bodies of the first and second thoracic vertebrae and multilocular expanding lesions with cortical thinning in both humeral heads. After some right hip pain in 1942 films showed changes in the right acetabulum. From 1942 to 1946 the patient was well, with hemoglobin 65 to 85 per cent, red

* The author is indebted for the use of this material to Dr. Philip D. Wilson and Dr. L. C. Mark of the Hospital for Special Surgery, New York, New York.

† The author has not seen this patient. He is greatly indebted to Dr. Lloyd Craver of New York for the data pertaining to this case, obtained from an abstract of the patient's hospitalization at Memorial Hospital, New York.

blood count 3.4 to 4.8 million, white blood count 4,000 to 4,600. In June, 1946, while on vacation, he noted the sudden onset of severe pain in the left shoulder radiating down the left arm; there was no swelling. Pain became intractable despite symptomatic therapy, and the patient became progressively weaker. He was hospitalized and received 6,000 cc. of whole blood in seven weeks, with transient supportive effect. Roentgenogram of the left shoulder was suggestive of malignant degeneration superimposed on old cystic disease and fracture, and the patient received two x-ray treatments to this region. This was followed by extreme, painful swelling of the entire left upper extremity, the skin of which was described as taut and glistening, with underlying brawny edema. The arm was held immobile at the shoulder.

On September 15, 1946, the patient entered the Memorial Hospital, New York. On admission he was described as a pale, chronically ill man looking older than his fifty-seven years. No pingueculae or lymphadenopathy were noted. The heart was slightly enlarged to the left, with a blood pressure of 140/70. A firm, non-tender spleen and liver edge could be palpated at the level of the umbilicus on the left and right, respectively. There were no other abnormal physical findings.

Laboratory examinations revealed: hemoglobin, 7.7 gm per cent; red blood cells, 2.7 millions; white blood cells, 4,200 with normal differential and one nucleated red blood cell seen. Blood indices, red blood cell fragility, reticulocyte count and sedimentation rate were normal. The platelet count was 140,000. Urine contained 1+ albumin and was negative for Bence-Jones protein. Blood Mazzini test was negative. Blood chemistry was as follows: blood urea nitrogen, 12.4 mg. per cent; fasting blood sugar, 167 mg. per cent; serum chloride, 97 mEq./L.; CO_2, 23.6 mEq./L.; serum proteins, 7.5 gm per cent; serum calcium, 8.9 mg. per cent; serum inorganic phosphorus, 3.9 mg. per cent; serum cholesterol, 146 mg. per cent total with 61 mg. per cent free; acid phosphatase, 0.77 units; alkaline phosphatase, 26.1 Bodansky units.

The patient's course was one of slow improvement after surgical drainage of the left axilla. A primary smear of exudate from this draining sinus, when stained by H. & E. and methylene blue, revealed many suggestive Gaucher cells. Sternal marrow aspiration revealed typical

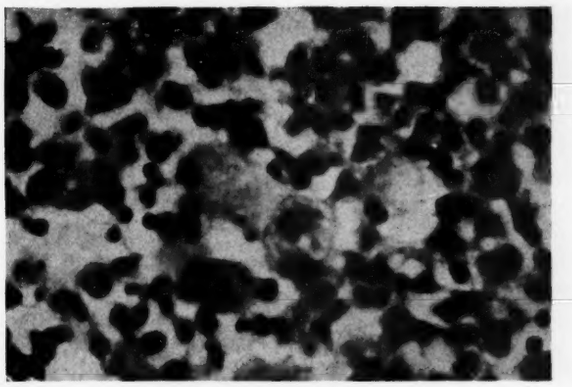


FIG. 4. An example of Gaucher cells from the sternal marrow of patient M. A., compare with Figure 1. Hematoxylin and eosin stain, × 1200.

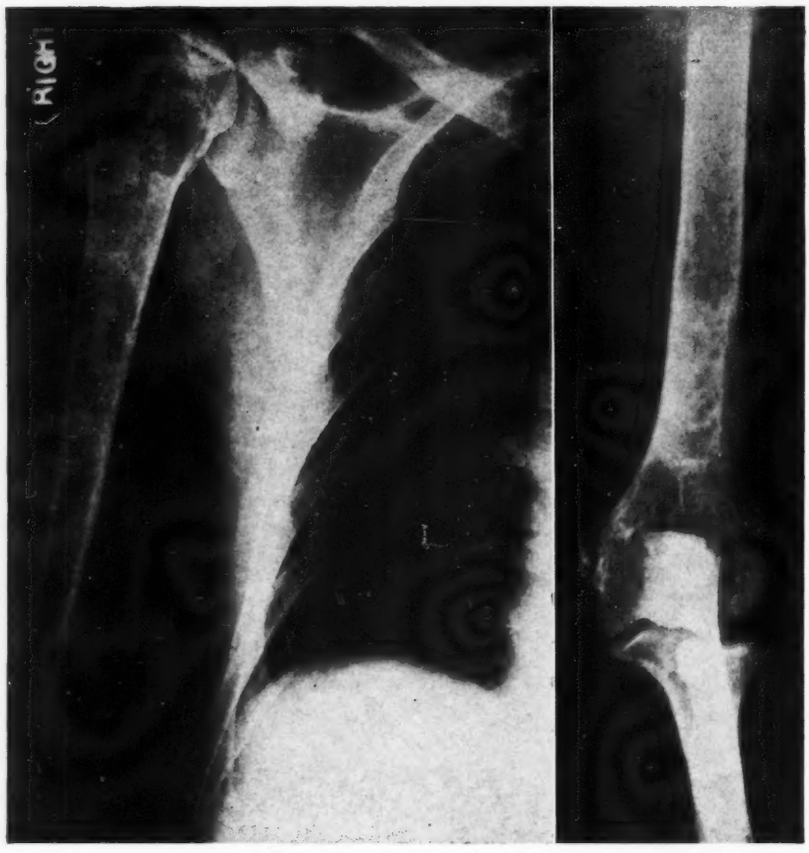
Gaucher cells. (Fig. 4.) On penicillin, symptomatic treatment and whole blood transfusions the patient improved steadily and was discharged on October 11, 1946. Review of all roentgenograms since 1938 revealed that the proximal (Fig. 5A) and distal (Fig. 5B) humeri, proximal and distal femurs (Fig. 5C), many ribs and the os coxae contained areas of radiolucency, some in a lattice-work pattern, together with cortical thinning which were suggestive of Gaucher's disease.*

At present the patient is in excellent general condition except for a few small draining sinuses in the left arm. He takes an active daily role in the running of his business.

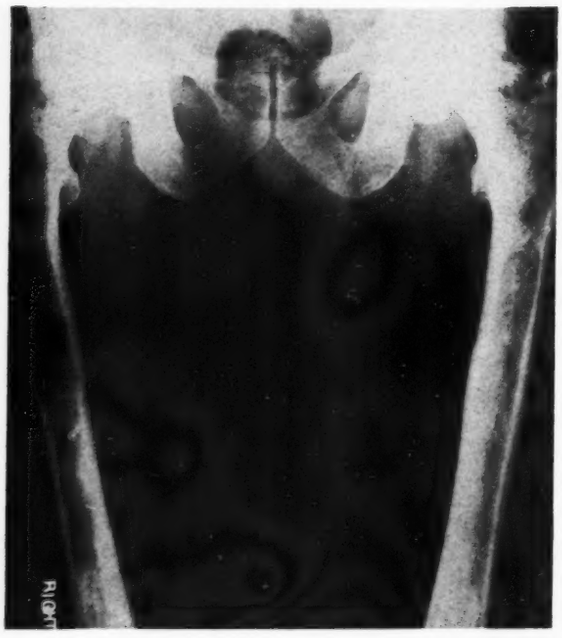
COMMENTS

Definition and Incidence. A rare, congenital, familial disorder of lipoid metabolism, Gaucher's disease usually occurs in siblings of one generation only,[1] as here. (A recent theory[2] suggests its hereditary transmission as a dominant mutant; evidence for this view is not convincing, and the occasional diagnosis of Gaucher's disease in more than one generation of a family is usually merely presumptive[2–7].) While it is generally held to be more common in females than in males, Atkinson[8] has shown that the sex incidence in a large series was approximately equal. The condition appears early in life but often escapes notice until late adult years because of its chronicity. More than half the cases in one series[9]

* The author is greatly indebted to Dr. H. O. Mosenthal of New York, New York, for the use of these roentgenograms.



5A 5B



5C

FIG. 5. Roentgenograms of patient M. A. A and B, right humerus; changes in the appendicular skeleton showing in addition to the endosteal scalloping an irregular widening of the medullary cavity. C, femurs; rather marked thinning of cortical bone in the right, and some evidence of sclerosis and irregular thickening in the left femur.

were recognized before the age of eight years, but cases as young as one week[10] and as old as seventy-nine years[11] have been described. A considerable proportion of those affected have been Jews, but the disease occurs in members of all races, including negroes[10,12] and orientals.[13]

Pathogenesis. Characteristic of the disorder is the distinctive "Gaucher cell" (Figs. 1, 3 and 5), collections of which are found packed within the spleen, bone marrow, liver and, less often, the lymph nodes. Long thought to contain kerasin, these cells have recently been shown to contain, at least in part, a cerebroside which differs from normal kerasin in containing glucose rather than galactose.[14–19] Conceivably, the aberrant lipoid metabolism may have produced a cerebroside so abnormal that it cannot be utilized in the usual manner.[20] The absence of demonstrable cerebroside in the serum and the normal amount and quality of red blood cerebroside[17] would seem to place the metabolic disorder within the reticulum cells and histiocytes rather than in the realm of intermediary lipoid metabolism.[21] The Gaucher cell fails to divide by mitosis and degenerates only very slowly.[22]

Clinical Aspects. Many of the characteristics of the adult form of Gaucher's disease are illustrated by Case I. Splenomegaly is an almost invariable finding, often moderate, usually slowly progressive; there is evidence that it begins in most cases at an early age. Hepatomegaly is a nearly constant sign in Gaucher's disease, probably beginning at a later date than the splenic enlargement. Even with tremendous hepatosplenomegaly the symptomatic disturbances are often strikingly slight. Peripheral lymph nodes are usually not enlarged although occasionally lymph node biopsy has led to the correct diagnosis.[10,23] Wedge-shaped, brownish pingueculae are frequent in older patients but rare in children. Ochre to brown skin pigmentation, with a yellow to leaden hue, is found in from 45 to 75 per cent of cases; the exposed parts are most frequently affected and a symmetrical pigmentation of the legs from just below the knees to the instep has been described.[24] Pick[25] believes that the pingueculae and skin pigment are expressions of a general hemochromatosis; other workers believe that hemosiderin is the pigment deposited. A high incidence of myopia and of malar flush has been claimed.[24] The hemorrhagic diathesis is relatively common, long-standing epistaxis[26] and bleeding from the gums being most frequently seen. Occasionally petechiae or purpuric spots are found but massive bleeding only rarely.[27] Pain in the limbs due to bone involvement (cortical pressure from medullary Gaucher cell collections) may develop in long-standing cases. Additional metabolic disturbances such as cholelithiasis (Case I) and diabetes mellitus (Case II) are said to occur frequently in "Gaucher families" both in the affected and in the normal siblings.

Laboratory Data. As with some other splenomegalies, a panhematopenia is frequently observed in Gaucher's disease. The anemia is usually moderate in degree and normocytic in type; there is little or no evidence of active blood regeneration.[28] Very rarely, splenomegaly is inconspicuous or absent[6,11,29] and anemia is the outstanding feature.[11] Leukopenia with normal differential count or relative lymphocytosis is the rule, and slight to moderate thrombocytopenia is common and has been held to be the cause of the hemorrhagic diathesis. The function of the swollen Gaucher liver, examined with the routine liver function tests, usually remains normal;[30] rarely is there evidence of marked hepatic dysfunction.[31] A number of patients with normal liver function and acholuric jaundice have been reported; this seems due to a hemolytic process without increased red blood cell fragility.[32–34] There are no characteristic abnormalities in the blood chemistry determinations. Except for a questionably low serum cholesterol value,[27,34] the total fats, cholesterol and lecithin of the blood have been found to vary within normal limits. In several cases the plasma lipoid nitrogen con-

centration has been elevated,[14,24,35] whereas the plasma lipoid phosphorus concentration has been normal;[24] this contrasts with true hyperlipemias in which the lipoid phosphorus as well as the lipoid nitrogen is increased.

Osseous Lesions. Risel[36] was the first to note macroscopic bone changes in Gaucher's disease, but it was Pick[25] who described in detail a form that is clinically and anatomically preponderantly osseous. He studied skeletal involvement in two brothers which was so generalized that scarcely a bone was spared. In the long bones the marrow cavity may be filled with yellow or gray, walnut-sized nodules of Gaucher cells impinging upon the still remaining marrow rests; a diffuse, tough mass of Gaucher cells may fill the marrow cavity like a plug, broken up partially by the still intact marrow substance. In the small, flat bones the markedly porous spongiosa may be filled with Gaucher cell collections. Gaucher cell infiltration of the vertebrae may reduce them to one-half or one-third their normal size, with shortening of body length and gibbus formation. Microscopically, one can see all stages of atrophy and disintegration of bone trabeculae due to pressure of the cell collections; some necrotic trabeculae are held together by relatively avascular fibrous tissue.

The first complete roentgenographic studies were made by Klercker[37] and Junghagen[38] in 1926. The latter author noted the following changes in Gaucher's disease: (1) well marked general osteoporosis; (2) porous and trabeculated spongiosa; (3) destruction of the spongiosa with the formation of large or small worm-eaten defects; (4) thinning of the cortex and widening of the long bones, particularly the lower end of the femur and (5) compression of diseased bones, particularly the head of the femur, by the weight of the body. Many believe that a widening of the lower ends of the femur just above the condyles (Fischer's sign) is the earliest as well as the most consistent change;[27,30,39,40] the bottle-shaped appearance has been likened to an Erlenmeyer flask. Bony changes occur frequently in the humerus, tibia, fibula, radius, ulna and ribs; changes in pelvis and vertebrae are mentioned less commonly. Figure 2B demonstrates changes in the small tubular bones of the hand. Involvement of the skull roentgenographically is exceedingly rare[41,42] and at least one report is open to question.[43] In addition to the characteristic mottled appearance of the expanded long bones with thin cortices, areas of cortical thickening signifying a reparative process may be noted;[31,40] occasionally the sclerosis is marked (Fig. 5B—this patient had an elevated serum alkaline phosphatase value). Pathologic fractures through the thinned compact bone are not uncommon and are usually associated with mild trauma; it is highly unusual for the cortex to be perforated by Gaucher cells[44] or for the periosteum to be involved. Occasionally the shafts of the long bones present a picture of apparently reduplicated cortex.

It is worthy of note that the large femoral lesion in patient P. S. was unaccompanied by any discomfort. Aching of the bones may occur and on occasion the swelling and tenderness may be a major complaint.[33] In rare instances[42,45,46,47] these signs have been so acute that the erroneous diagnosis of osteomyelitis has been made; the finding of sterile pus, low grade fever and lack of leukocytosis should cast doubt upon this diagnosis. Weight-bearing compression of the diseased femoral head might be confused roentgenographically with Legg-Perthe's disease, tuberculous coxitis, chronic osteomyelitis or "atypical neurotrophic joint."[33] Caisson disease, senile osteoporosis, osteitis fibrosa cystica and multiple malignant bone metastases have all been considered in differential diagnoses; vertebral destruction and gibbus formation should be differentiated from Pott's disease by the intact intervertebral disc. In Case 1 the diagnosis of giant-cell tumor of the femur was seriously entertained.

Pathology. There is no direct relation between the intensity of the Gaucher cell deposits and the duration of the disease. The spleen on the average is increased

tenfold in size and has been known to weigh 8,100 gm. The kerasin may constitute 6 to 10 per cent of the weight of the dried spleen.[48] Pick considers the Gaucher spleen to show an apparent and complete functional differentiation between endothelial and reticulum cells; the Gaucher cells arise from the reticulum cells and contain little or no hemosiderin, while the venous sinus endothelium contains no Gaucher substance but hemosiderin in considerable amount. The splenic pulp is almost entirely replaced and the Gaucher cells are found also in the Malpighian corpuscles. Pigment, chiefly hemosiderin, increases as the disease progresses.

The liver is often twice normal size. Small, pale areas grossly suggest leukemic infiltration; microscopically, the portal spaces and sinusoids contain Gaucher cells. A peculiar disintegration of liver architecture and thickening of Glisson's capsule can be distinguished from the usual cirrhosis by syncytial bundles of Gaucher cells in the connective tissue and by absence of bile duct and (antecedent) connective tissue proliferation.

Bone marrow disturbance has been seen by roentgen examination in more than half the cases. The peculiar tendency of Gaucher cells in marrow to elongate and become spindle-shaped is thought to be due to a fascicular type of growth rather than to the effect of compression.

The deep lymph nodes are more likely to be enlarged than the superficial nodes; the amount of pigment is usually greater than in the spleen and liver.

In infants a rapid and malignant course of Gaucher's disease has been observed, with neurologic signs (chiefly cerebral) and early death.[49,50] This may be due to the presence of Gaucher substance in the pyramidal cells of the cerebral cortex. Pigment is absent in infants and children. That the thymus, tonsils and intestinal lymphatics of infants may contain Gaucher cells is explained by the fact that the reticulum cells of these organs are phagocytic during the first year of life.

In one adult case the distal lymphatic system of the lungs[51] and in another a small area in the kidney[9] contained Gaucher cells. Biopsy of a typical pinguecula has revealed Gaucher cell infiltration.[52]

Diagnosis. The clinical picture of splenomegaly with pingueculae, pigmentation and good physical preservation is often distinctive enough to make the diagnosis, and bone lesions by roentgenogram lend further support. The diagnosis, however, can be considered as certain only if the presence of Gaucher cells is demonstrated. Marrow aspiration demonstrates their presence and has replaced splenic or liver puncture as the procedure of choice; the latter procedures are often contraindicated by a hemorrhagic diathesis. Splenectomy, when performed, will give the diagnosis on microscopic section.

Prognosis. Except in infants or in terminal stages cachexia is slight or absent. There is no correlation between intensity and duration of the disease process. Death has usually resulted from intercurrent infection, often pneumonia, but most reported cases antedate the newer chemotherapeutic agents. In infants the onset is more acute, and neurologic symptoms (rigidity of the neck, convergent strabismus, opisthotonos) as well as retardation of development may be noted; the infantile disease is often fatal[53,54]

Treatment. There is no specific treatment for the disease. Liver extract is believed to have helped one patient,[12] but there has been no subsequent enthusiasm for the suggestion. X-ray radiation to the spleen seems a poor measure because it increases the anemia; there is no evidence that such therapy to the skeleton is of benefit. Splenectomy, first performed for Gaucher's disease in 1895,[55] remains the most hopeful palliative measure, the principal objection being its high mortality. There is a conviction, possibly based on the first ten recorded splenectomies for Gaucher's disease,[56] that the operative risk is 20 per cent. However, Whipple[57] reported but ten deaths in 106 splenectomies performed at his Clinic for various reasons. Since the Gaucher spleen

while enormously large is one of the easiest to remove because it is rarely adherent, the current mortality rate must be much less than 20 per cent.

There has been a theory supported by many[25,27,31,37,58] that splenectomy hastens the onset and spread of bone involvement. However, a greater number[26,33,34,42,47,51,59,60,61] can find no support for this view, and it must be admitted that the immediate effect of splenectomy in exsanguinated children is often strikingly beneficial.[59,60] In occasional cases pingueculae[34] and pigmentation[34,61] disappeared postoperatively. Splenectomy would seem to have definite palliative value for (1) burdensome weight of the organ, (2) anemia and (3) hemorrhagic diathesis; the red blood cell count and platelet count may be expected to rise after the operation.

SUMMARY

Two cases of the so-called osseous form of Gaucher's disease occurring in siblings have been presented. The pertinent literture has been reviewed briefly concerning the clinical and laboratory findings, roentgenographic picture, pathogenesis, pathology, diagnosis, prognosis and treatment of this disorder.

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Review

Role of Sympathetic Blockade in the Therapy of Hypertension*

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DURING the past few years considerable progress has been made in the development of agents capable of producing a specific and effective blockade of responses to sympatho-adrenal activity. Research on several series of blocking agents has progressed to the point where it is now possible to produce a clinically useful "chemical sympathectomy." Such a chemical sympathectomy has obvious uses in the clinical evaluation and treatment of conditions in which a large component of sympathetically mediated smooth muscle spasm is involved. However, any assessment of the place which these agents may ultimately occupy in the therapy of hypertension depends upon a more specific delineation of the role of the sympatho-adrenal system in human hypertension. In spite of extensive laboratory and clinical investigation and elaborate speculation this role is still obscure.

In his Janeway lecture of 1941[77] Page listed fifty-two types of human hypertension. These were classified with respect to etiology with two notable exceptions, namely, essential hypertension and malignant hypertension. Unfortunately, about 95 per cent of all cases of human hypertension fall into these two poorly defined groups. Indeed, it is quite possible that neither of these categories is homogeneous. Inasmuch as the etiology of most cases of human hypertension is still unknown, no rational basis has yet been established for the use of adenergic blockade in their treatment.

Experimental neurogenic hypertension has been known and studied for many years. Some of the more prominent features of this type of hypertension are listed in Table 1. Even a casual appraisal of these characteristics indicates that human essential hypertension and uncomplicated neurogenic hypertension have little in common. Hypertension induced by infusion of epinephrine or nor-epinephrine is included for comparison. It is clear that infusion of epinephrine causes hemodynamic changes which are quite different from those seen in essential hypertension and which resemble those observed in neurogenic hypertension. Infusion of nor-epinephrine,[36] on the other hand, induces changes comparable to those observed in essential hypertension. However, the similarity has not been proved to be of etiologic significance. Hypertension with these characteristics may be duplicated by the infusion of any agent, e.g., angiotonin which produces a generalized peripheral vasoconstriction which predominates over cardiac stimulation.

Because of the many dissimilarities between human essential hypertension and experimental neurogenic hypertension studies of the latter have been relegated to the background in recent years in favor of work on experimental renal hypertension which much more closely resembles essen-

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tial hypertension.[11,35,64,78] (Table I.) Nevertheless, a careful analysis of neurogenic hypertension is important as a basis for the recognition or exclusion of neurogenic factors in human hypertension.

Many clinical observations indicate that neurogenic factors in some way influence the development and maintenance of essential hypertension. It has long been recognized that stressful situations may induce marked increases in both systolic and diastolic pressures which persist for varying periods of time[21,38] and that hypertensives tend to have a characteristic type of personality.[2,99] Such individuals usually exhibit important components of repressed antagonism and anxiety. They do not find emotional outlets in overt acts, but instead their emotions are expressed through an increased activity of the sympatho-adrenal system with a consequent increase in blood pressure. Relief of psychic tension frequently produces salutary effects in these patients. It has also been observed that individuals who show hyperactive sympathetic vasomotor reflexes (as measured by the cold pressor test) are much more prone than the average individual to develop hypertension in later life.[57]

Figure 1 illustrates the principle nervous pathways involved in the maintenance of blood pressure. Under normal conditions the afferent pathways from the carotid sinus and aortic arch areas carry tonic impulses which depress the activity of the vasomotor centers. Consequently, section of these moderator nerves in animals[51,56] or man[103] brings about a sustained hypertension. Of more importance to an analysis of clinical hypertension, however, is the fact that increased activity of the sympatho-adrenal system may arise on a central basis.

TABLE I

CARDIOVASCULAR CHARACTERISTICS OF VARIOUS TYPES OF HYPERTENSION

Indices \ Mechanism	"Essential" Hypertension	Renal Hypertension	Neurogenic Hypertension	Epinephrine Infusion	Non-epinephrine Infusion
Pulse rate	N	N	↑	↑	N or ↓
Cardiac output	N	N	↑	↑	N or ↓
Total peripheral resistance	↑	↑	N	↓	↑
Blood flow in extremities	N	N	↑	↑	↓
Pressure fluctuations	Marked early Limited late	Limited	Marked	Controlled	Controlled

N = Normal ↑ = Increased ↓ = Decreased

In animals such hypertension may be induced by electrical stimulation of or injury to the hypothalamus.[59,98] Also, in both animals[17,26,39] and man[16] it may result from an increased intracranial pressure, at least in part, because of the cerebral ischemia which results.[16,48]

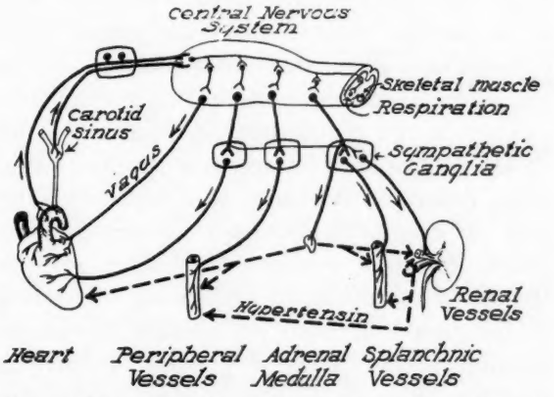

FIG. 1. Diagrammatic representation of the principal nervous and humoral pathways involved in the maintenance of systemic arterial pressure. Solid lines depict nervous pathways and broken lines humoral agents.

Neurogenic renal vasoconstriction with consequent activation of the renin-angiotonin mechanism is not a major factor in most cases of neurogenic hypertension; evidence for this is seen in the limited fall in blood pressure which follows renal de-

nervation[41,54] and the failure of prior nephrectomy to alter the pressor response to moderator nerve section.[95] However, neurogenic renal vasoconstriction may be adequate to produce a sustained hypertension after other body structures have

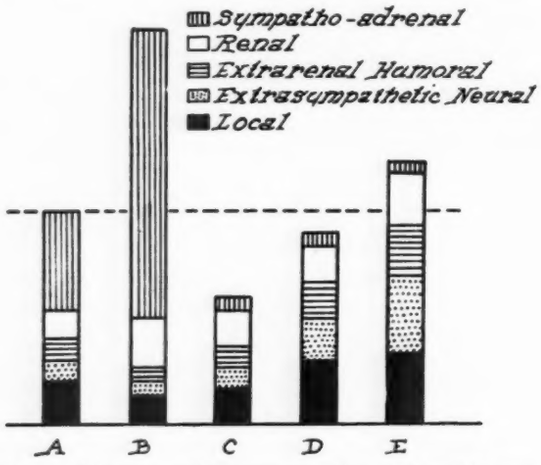

FIG. 2. Diagrammatic representation of possible contributions of various factors to the maintenance of the systemic arterial pressure during neurogenic hypertension and its subsequent "cure" by sympathectomy or adrenergic blockade. A, normal; B, neurogenic hypertension; C to E, sequential stages in the recovery of the blood pressure after sympathectomy. The pressure may stabilize at either D or E.

been sympathetically denervated[40,44] and it is possible that neurogenic renal vasoconstriction may play a significant role in the development of essential hypertension.

One of the distinguishing characteristics of uncomplicated neurogenic hypertension is its dramatic response to sympathectomy and to chemical blockade of the sympathetic nervous system. Complete sympathectomy results in an immediate reduction in the blood pressure to normal or to subnormal levels, with a gradual return to normotensive or slightly higher levels over a period of one to two months.[40,41,54] Moderator nerve section or increased intracranial pressure usually fails to increase the blood pressure in completely sympathectomized animals; and if a rise is elicited, it is relatively slight and develops slowly.[5,27,41]

Consistent lowering of the blood pressure has been observed in dogs with neurogenic hypertension to whom ergotamine, 883F or 933F has been administered.[9,52,53,59,60] In some of these cases central inhibition of vasomotor activity as well as adrenergic blockade by the drug was undoubtedly involved. However, this does not detract from the fact that the reduction or elimination of sympatho-adrenal activity always induces a dramatic reduction in blood pressure.

Factors involved in the regulation of the blood pressure of normal[5,13,46,65] and neurogenic hypertensive animals after complete removal of the sympathetic nervous system have not been clearly defined. However, these factors may include renal humoral,[3,28,55,97] extrarenal humoral,[6] extrasympathetic neural[4,5,40,46] and local[22] components; all are important in any evaluation of the blood pressure response to sympathectomy or to sympathetic blocking agents. The degree of fall in blood pressure after these procedures may depend not only upon the extent to which the sympatho-adrenal system was involved in the maintenance of the initial pressure but also upon the rapidity and the extent of compensation by other factors. Figure 2 illustrates a possible sequence of adjustments during the development of neurogenic hypertension and its subsequent "cure" by sympathectomy or sympathetic blockade. It must be remembered that few quantitative data are available regarding most of these factors. However, it is clear that some such over-all adjustment does occur.

In contrast to neurogenic hypertension, the role of adrenergic factors in experimental renal hypertension is obscure. The sequence of events by which interference with renal hemodynamics leads to elevation of the systemic blood pressure has been carefully studied and has been shown to be independent of nervous mechanisms.[11,35] Sympathectomy does not prevent the development of renal hypertension and induces only slight and irregular reductions in pressure in renal hypertensive animals.[3,28,55,97]

Prolonged administration of adrenergic blocking agents may produce a significant but highly variable reduction in systemic arterial pressure in animals with experi-

mental renal hypertension. This has been observed after the oral administration of yohimbine to dogs,[58] the oral administration of dibenamine® to rats[71] and the intravenous administration of dibenamine® to dogs.[100] In none of these experiments involving chronic administration of adrenergic blocking agents were the pressures consistently reduced to the normotensive range. Single injections of 883F and 933F produce little or no vasodepression in dogs with chronic renal hypertension,[9,20,61] a response very similar to that seen in normotensive controls. It has been reported that single injections of pentobarbital, yohimbine and 883F, but not 933F, produce a greater depressor response in rats which have been hypertensive for more than two months than in those with a shorter duration of hypertension;[84,86] on this basis it has been suggested that neurogenic factors are of importance in late but not in early renal hypertension.[76,84,86] This differential response with regard to the duration of the renal hypertension was not observed with dibenamine® in chronic experiments on rats[71] or with various anesthetics and other procedures to reduce vasomotor activity in experiments on dogs.[68] In general, the significance of those observations which indicate a correlation between the duration of experimental renal hypertension and the magnitude of the adrenergic component seems to be very limited.[70,71]

Other evidence which has been adduced to support the significance of neurogenic factors in renal hypertension is the observation that the arterial pressures of normal and renal hypertensive dogs and rabbits were reduced to essentially the same level after complete destruction of the central nervous system.[18,19] However, interpretation of the results obtained with this drastic procedure is difficult. Other workers have observed a sharp fall in pressure when the spinal cord was destroyed below C_5 in renal hypertensive dogs but the pressures returned to hypertensive levels as the acute effects of the operation wore off.[32] Other experiments involving elimination of the central connections of the sympathetics by cervical cord section in the region of C_7 have demonstrated that the pressures of early and late neurogenic hypertensive dogs may fall below those of normal dogs after cord section. This is probably due to a reduction in non-sympatho-adrenal pressure factors in these animals. (Fig. 2, B.) However, under the same conditions pressures of renal hypertensive animals are maintained significantly above those of the normals.[42] In addition, it has been demonstrated that chronic destruction of the spinal cord below C_5 does not prevent the development of typical chronic renal hypertension.[33] It appears that the less trauma involved in the surgical elimination of the sympathetic nervous system in animals with renal hypertension, the less effect the procedure has on the blood pressure.

In human essential hypertension also, sympathectomy or blockade of the sympatho-adrenal system brings about an equivocal response. There is little doubt that various degrees of surgical sympathectomy may produce a prolonged reduction in blood pressure in certain selected cases[43,81,82,89] but the response is highly variable, and the degree of benefit attributed to the procedures employed may depend to a considerable extent upon an evaluation of the natural course of the disease.[79]

In the work of Goldenberg and coworkers[37] who employed members of the Fourneau series of adrenergic blocking agents to detect pheochromocytoma it was observed that most patients with essential hypertension actually responded with an increase in the resting blood pressure. This increase was undoubtedly due to the stimulant effects of these drugs on the central nervous system[70] but failure to respond by a fall in pressure sharply distinguished cases of essential hypertension from those in which the rise in blood pressure was largely due to an excessive secretion of epinephrine or nor-epinephrine. Clinical treatment of hypertension with the more effective adrenergic blocking agents has also produced highly variable results which will

be discussed hereafter in connection with the individual compounds involved.

The highly variable blood pressure responses to adrenergic blockade in cases of experimental renal hypertension and human essential hypertension, particularly those responses obtained with single injections of blocking agents, are extremely difficult to interpret. However, their marked irregularity when compared with the consistent depressor response to adrenergic blockade seen in neurogenic hypertension argues against derangement of sympatho-adrenal function as a major factor in experimental renal hypertension and most cases of established essential hypertension. In addition, it must be concluded that the contention that nervous factors are of importance in late but not in early renal hypertension has not received convincing support from experiments employing sympathetic denervation and adrenergic blocking agents.

Although blood concentrations of vaso-excitor material (VEM) are increased in both experimental renal and human essential hypertension,[88] studies of this material have not progressed to the point at which its role in maintaining the elevated blood pressure can be adequately evaluated. This vaso-excitor material seems to have little direct effect on smooth muscle and produces its primary effects not directly but by sensitizing vessels to the action of epinephrine and probably to that of sympathin. Failure of such powerful adrenergic blocking agents as dibenamine® consistently to reduce to normal the pressure in renal and human essential hypertension argues against vaso-excitor material playing a major role in maintaining the elevated blood pressure in these conditions.

None of the specific adrenergic blocking agents inhibits vascular responses to angiotonin,[70] and the mechanism by which adrenergic blockade or sympathectomy brings about even a partial reduction in blood pressure in renal or human essential hypertension has not been clearly established. However, it has been definitely demonstrated that vasomotor reflexes are still active in the presence of acute or chronic renal hypertension in animals,[7,19,68,97] man[83] and in human essential hypertension.[31,83] Consequently, it may be assumed that at least part of the observed decrease in pressure is due to the elimination of sympatho-adrenal factors. If a significant element of neurogenic renal vasoconstriction is involved in human essential hypertension, a second factor in the hypotensive effect of adrenergic blockade may be the increase in renal blood flow which could be induced by the blockade. Inhibition of sympathetic vasoconstrictor tone by high spinal anesthesia has been shown to cause an increase in renal blood flow in both human essential hypertension and experimental renal hypertension in dogs[94] but the relation of this observation to the etiology of the blood pressure elevation is not clear. Sympathectomy may fail to alter renal blood flow and filtration in at least some cases of essential hypertension.[15] As previously pointed out, the fall in pressure elicited by the elimination of neurogenic factors may not be directly proportional to the magnitude of these components but may also be dependent upon the extent to which other factors compensate for the deficiency.

Possible interrelationships of various hypertensive factors in renal (and perhaps essential) hypertension are diagrammed in Figure 3. It must be recognized that the highly variable response of renal and essential hypertension to sympathectomy or sympathetic blockade makes it impossible to present any diagram adequately covering all cases. Column C represents a case in which sympathetically mediated renal vascular tone is assumed to be a significant factor in maintaining the elevated pressure; column D depicts possible changes in the few cases of human essential hypertension in which a continued fall in pressure is noted for some time after sympathectomy, perhaps also on the basis of altered renal blood flow. Column E represents a common result of sympathectomy or adrenergic blockade in renal and essen-

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tial hypertension; this result may or may not be preceded by some early fall in pressure such as illustrated in column C.

On the basis of the aforementioned it would appear that the role of adrenergic blockade in the treatment of hypertension, with the exception of isolated cases clearly due to sympatho-adrenal factors, is negligible. However, the possibility remains that neurogenic factors may be involved in the early stages of human essential hypertension. As previously mentioned, certain psychic components are known to be involved in the development of hypertension and it is possible that emotionally activated neurogenic factors may cause repeated episodes of renal vasoconstriction and ischemia which finally lead to the development of local organic changes capable of permanently altering renal hemodynamics. The experimental basis for such a conclusion is as yet incomplete but certain points of evidence are of interest in this connection.

It has been observed that reflex activation[40,44] or electrical stimulation[62,63] of sympathetic nerves to the kidney may cause sufficient vasoconstriction to produce marked hypertension. However, in experiments which involved stimulation for twenty to twenty-two hours per day for as long as forty-five days the hypertension persisted only during and for a few hours after the end of stimulation. It has also been frequently observed that experimental hypertension may itself bring about marked changes in the renal vessels.[29,34,50,87,101] In cases of unilateral compression of the renal artery or kidney parenchyma vascular changes in the contralateral kidney may alter its hemodynamics to such an extent that it becomes capable of maintaining the hypertension after surgical removal of the kidney initially involved. It is not surprising that many workers have noted a persistence of hypertension after removal of a single ischemic kidney.[29,47,80,101]

A similar sequence of renal changes has not been demonstrated in connection with neurogenic hypertension. However, highly suggestive evidence for the development of persistent hypertension on the basis of intermittent neurogenic vasoconstriction is found in observations on rats subjected to repeated audiogenic stimuli.[24,66] The blood pressures of young control and stimulated rats were found to be essentially the same

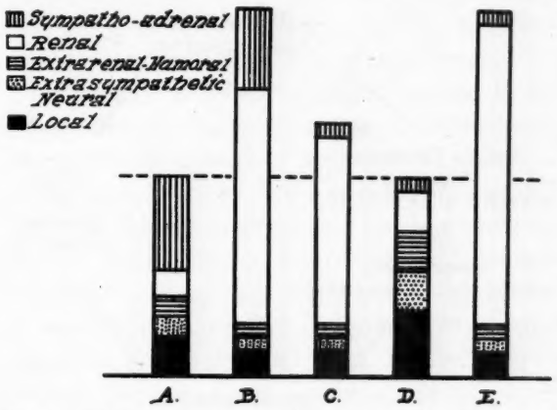

FIG. 3 Diagrammatic representation of possible contributions of various factors to the maintenance of the systemic arterial pressure during renal (and perhaps essential) hypertension. A, normal; B, renal (and perhaps essential) hypertension; C, immediately after extensive sympathectomy; D, case of essential hypertension in which the pressure continued to drop after sympathectomy, presumably because neurogenic alteration of renal blood flow was a significant factor in the original hypertension; E, a common end result of sympathectomy which may or may not be preceded by an initial fall in pressure such as that depicted in C.

but it was noted that a large percentage of the experimental animals became hypertensive after they were one year of age. Hypertension was noted particularly among those which had consistently responded vigorously to the stimuli. It is of particular interest that these responses are characterized by a marked sympatho-adrenal discharge including mydriasis, piloerection, etc.[23] Although blood pressure was not determined in these studies, it is reasonable to assume that a temporary elevation accompanied each response.

One may speculate that a similar process occurs in some humans. During early stages of the development of hypertension the individual may be subjected to repeated episodes of increased pressure and renal vasoconstriction on a purely neurogenic (psychic) basis and over a period of years may secondarily develop sufficient renal

hemodynamic changes to sustain a relatively stable, renal hypertension. Such a sequence of events would explain the lability of early and the stability of late hypertension as well as the observed correlation between psychic and sympatho-adrenal factors and the final development of a largely non-neurogenic hypertension.

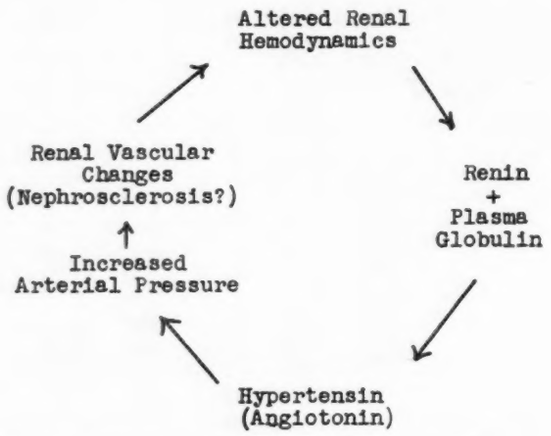

FIG. 4. Sequence of events by which renal hemodynamic alterations induced by mechanical or neural factors might lead to a persistent, self-perpetuating renal hypertension. Sympatho-adrenal factors could enter this cycle by increasing the arterial pressure or directly altering renal hemodynamics.

A sequence of events by which renal hemodynamic alterations induced by either mechanical or neural factors might lead to persistent, self-perpetuating renal hypertension is depicted in Figure 4. The hemodynamic changes in the kidney might be dependent upon organic changes in a majority of renal vessels or simply upon a redistribution of renal blood flow leading to a relative cortical ischemia.[96]

In summarizing evidence for the participation of deranged sympatho-adrenal ("neurogenic") factors in human hypertension it must be concluded that such factors have been conclusively demonstrated only in cases of pheochromocytoma, trauma to the central nervous system and increased intracranial pressure. However, there is presumptive evidence to indicate that neurogenic factors may be important during the early, labile phases of essential hypertension and that the effects of this early sympatho-adrenal activity may lead to persistent hypertension on a renal basis later in life. It should be emphasized, however, that the development of hypertension through this or any other mechanism occurs only in individuals predisposed by some completely unknown but probably hereditary influence.

In the treatment of neurogenic factors in hypertension, peripheral vascular disease, etc., it is necessary to inhibit the excitatory, vasoconstrictor effects of sympatho-adrenal activity. Blockade of inhibitory effects of the sympatho-adrenal system and of other nervous activity is not only unnecessary but also frequently undesirable. Chemical blockade may occur at many points along the reflex arcs controlling the activity of the sympatho-adrenal system. (Fig. 1.) However, in order to achieve a desirable degree of specificity it is necessary to produce the blockade at the efferent neuro-effector junction. Blockade within the central nervous system, along peripheral nerves or at autonomic ganglia inevitably affects nervous functions other than excitatory activity of the sympatho-adrenal system. Blockade within the central nervous system alters many vital regulatory reflexes, respiratory activity and particularly vagal activity, even when consciousness is not impaired. Blockade at autonomic ganglia indiscriminately interrupts all efferent impulses passing over both the sympathetic and parasympathetic pathways.

Agents which block responses of effector cells to sympatho-adrenal stimuli may be termed adrenergic blocking agents. It is only at these effector cells that adrenergic mediators are involved in transmission of the nerve impulse. For a number of reasons the frequently used terms "adrenolytic" and "sympatholytic" agents are ambiguous and undesirable.[70]

Efforts to develop pharmacologic agents capable of preventing excitatory responses to sympatho-adrenal activity have led to the study of a wide variety of compounds. The search for new agents has been spurred by the fact that none of the currently avail-

able agents is wholly satisfactory. Until very recently their use in both research and therapy was seriously limited by lack of specificity, incompleteness of blocking action and high toxicity. The characteristics of an adrenergic blocking agent capable of producing a useful "chemical sympathectomy" are a high specificity, a blockade effective against strong stimuli, a prolonged and uniform action and a high therapeutic index. Much has been said and written about the potency of various blocking agents but this property seems to be of little importance in comparison with a high therapeutic index. Some of the most potent compounds available at the present time have the lowest therapeutic indices, particularly because of their stimulating effects upon the emetic center.[70]

The β-haloalkylamines, of which dibenamine® may be considered the prototype, are the most recently discovered and also the most effective, specific and persistent of the presently known adrenergic blocking agents.[70,72,73,75] These compounds apparently block by a direct chemical combination with some substance in the effector cell and thereby prevent responses to adrenergic mediators.[74] Because of the stable nature of this bond these agents have a very prolonged action. Certain members of the group block responses of smooth muscle cells to histamine.[70] Except for this action the blockade produced seems to be limited almost entirely to the excitatory effects of adrenergic stimuli. These agents produce a transient stimulation of the central nervous system but this effect wears off much more rapidly than the adrenergic blockade and is primarily associated with a high concentration of the drug in the blood stream such as may occur after rapid intravenous injection.[69] Central nervous stimulation can be almost completely eliminated by slow administration or prior sedation; for example, the LD_{50} for mice is about 50 mg./kg. when dibenamine® is administered intravenously within a few seconds but animals may survive doses as high as 300 mg./kg. when the injection is made over a period of one-half hour. The drugs are effective by all routes of administration but when administered subcutaneously, intramuscularly or intraperitoneally their local irritant action may produce tissue necrosis.

Dibenamine® has been employed in the diagnosis and preoperative therapy of pheochromocytoma with excellent results.[90,91] The pressor response evoked by the histamine test in these patients is completely blocked and reversed and the injection of dibenamine® at seventy-two-hour intervals has been found to provide complete symptomatic relief. In human essential hypertension, therapy with dibenamine® produces a very significant fall in both systolic and diastolic pressures in some patients.[12] In severe hypertension, particularly the malignant form, the drug has been found to lower the blood pressure significantly in most cases but rarely to return it to the normotensive range. However, striking relief of sequelae such as hypertensive encephalopathy and impaired renal function was noted in most cases,[102] probably due to the release of local vascular spasm.

Other workers have observed a significant depressor response to dibenamine® lasting twenty-four to seventy-two hours in many patients with early or moderately advanced benign hypertension but not in patients with more advanced organic cardiovascular changes.[49] On this basis it was suggested that the response to dibenamine® should be determined for prognostic purposes prior to sympathectomy as a measure of the role of the sympatho-adrenal system in a given case of hypertension.[49,102] On theoretical grounds an agent with the specificity of dibenamine® would be expected to be ideal for this purpose. Indeed, attention has been called to the similarity between the over-all effects of dibenamine® medication and those of surgical sympathectomy.[100] It has also been reported that dibenamine® is superior to tetraethylammonium as a test for predicting the results of sympathectomy in acute peripheral vascular conditions but the same investigator questioned its

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prognostic value in hypertension.[14] As previously mentioned, lack of knowledge regarding the etiology of human essential hypertension and the multiplicity of factors determining the extent of the fall in blood pressure after excision or blockade of the sympathetic system makes the interpretation of any prognostic test extremely hazardous. Results of tests with priscoline,® the ergot alkaloids, tetraethylammonium, spinal anesthesia and barbiturates in which factors other than peripheral blockade of the sympatho-adrenal system are involved would seem to have even less diagnostic specificity than tests with dibenamine.®

Significant toxicity, primarily central nervous system excitation, and the necessity for slow intravenous administration or prior sedation have considerably limited the study of dibenamine® in the therapy of hypertension. However, recent reports have indicated that other members of this series possess up to ten times the potency of dibenamine® without being more toxic.[70,74] This increased therapeutic index perhaps coupled with the increased oral absorption of some congeners[25] may largely eliminate the present difficulties and disadvantages of the β-haloalkylamines. It is possible that within the next few years a truly satisfactory clinical agent will be found within this series of adrenergic blocking agents.

Recently, significant advances have resulted also from the study of adrenergic blocking agents of the ergot alkaloid series. Stoll has demonstrated that "ergotoxine" is really a complex of three alkaloids, namely, ergocornine, ergocristine and ergokryptine.[92] He has also succeeded in producing dihydro derivatives of all these compounds.[93] Pharmacologic tests indicate that all members of the ergotoxine complex are more potent adrenergic blocking agents than the commonly employed ergotamine and that hydrogenation also markedly increases the potency of all these alkaloids.[70,85] Members of the ergotoxine complex differ from one another only in possessing different amino acids in the polypeptide side-chain of the lysergic acid nucleus. No unnatural polypeptide-containing ergot alkaloids have yet been reported but the synthesis of alkaloids containing different amino acids would seem to be a promising line of approach in this field.

Although the ergot alkaloids are true adrenergic blocking agents, they unfortunately also have very potent effects upon the central nervous system.[70] All known natural and dihydrogenated members of this group act on the central nervous system to depress reflexes in concentrations lower than those required to produce true adrenergic blockade. Another expression of their central action is the vomiting which they produce in humans in total doses as low as 0.3 mg.;[10,30] hypertensive patients are more sensitive than normal individuals to the emetic action of the dihydro alkaloids.[10] Because of the serious limitation in dosage imposed by stimulation of the emetic center production of significant adrenergic blockade in humans with any of the natural or dihydrogenated ergot alkaloids has not yet been demonstrated.

However, even in the absence of adrenergic blockade the ergot alkaloids are capable of inducing some reduction in blood pressure in human essential hypertension.[10,30] This fall in pressure appears to have two components: (1) the central stimulant effect of the alkaloid on the vagal center to decrease heart rate and cardiac output and (2) a central depression of the cardiovascular reflexes which normally compensate for changes in body position. Because of this second factor the orthostatic hypotension caused by the ergot alkaloids cannot be considered as evidence for a "sympatholytic" action, i.e., the production of adrenergic blockade. In hypertensive patients reduction in arterial pressure by these agents has been found not to parallel the suppression of experimentally induced vasomotor reflexes; in many cases an increase in the dose of an ergot alkaloid causes an increase rather than a decrease in pressure.[10] It is interesting to note that the pulse pressure is

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markedly decreased during the fall in blood pressure induced by the dihydro ergot alkaloids in hypertensive patients; an unaltered or increased pulse pressure would be expected if the fall were primarily due to adrenergic blockade with resultant peripheral arteriolar dilatation.

A third group of adrenergic blocking agents which has recently received attention is the imidazolines. These drugs are moderately effective in causing adrenergic blockade but they exhibit many important side effects.[70] Priscoline,® the most thoroughly studied member of the series, in addition to producing adrenergic blockade stimulates almost all smooth muscles and its effects are comparable in one way or another to those of sympathomimetic, parasympathomimetic and histaminergic agents. In the few cases of human hypertension in which priscoline® was given little reduction in blood pressure was observed.[1,45] although the agent is capable of producing significant adrenergic blockade and direct peripheral vasodilatation in doses tolerated by humans.[45] The basis for the failure of the drug to reduce blood pressure is probably that priscoline® is a potent cardiac stimulant; the increase in cardiac output may balance or more than compensate for the vasodilatation produced. Even a massive dose of priscoline® taken with suicidal intent caused no lowering of blood pressure.[67] Indeed, priscoline® may actually cause an alarming increase in blood pressure in some patients.[8]

SUMMARY

The role of adrenergic blockade in the therapy of hypertension is still obscure. Pharmacologic advances during the last few years have led to the development of agents capable of producing a clinically useful "chemical sympathectomy." Such agents are very effective in lowering the blood pressure in cases of neurogenic (sympatho-adrenal) hypertension.

At the present time pheochromocytoma and intracranial lesions are the only causes of human hypertension which are definitely known to involve overactivity of the sympatho-adrenal system. However, presumptive evidence is accumulating to indicate that neurogenic factors may be involved in early essential hypertension and it is possible that adequate adrenergic blockade early in the course of such hypertension may be effective in aborting its development. Only additional evidence regarding the etiology of essential hypertension and further clinical trial of adrenergic blockade can define the extent to which this possibility may be realized.

Of the compounds currently employed for the production of adrenergic blockade, the β-haloalkylamines appear to be the most promising. They are the most specific, effective and persistent of the available agents. The dihydro ergot alkaloids are much more effective than their non-hydrogenated congeners. However, at present much of the experimental work on these compounds is complicated by the marked depressant effects which they exert upon vasomotor reflexes and the vasomotor center and by their stimulant action on the vagal nuclei. The clinical administration of the dihydro compounds has been seriously limited by their very potent emetic action. Significant specific adrenergic blockade has not yet been produced in humans by members of the ergot series. A third group of adrenergic blocking agents to receive recent attention, the imidazolines, appear to cause so much cardiac stimulation that no consistent lowering of the blood pressure is observed when they are administered to either animals or man.

It should be emphasized that research in the field of adrenergic blockade need not be limited to members of series now known to be active. The three groups of the aforementioned compounds are structurally unrelated; only four years ago the β-haloalkylamines were completely unknown as adrenergic blocking agents. The cooperation of synthetic chemists and pharmacologists in the study of series of compounds unrelated chemically to those listed here may provide the solution in the search for

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an agent producing a fully satisfactory "chemical sympathectomy."

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Seminars on Cancer Research

Carcinogens and Carcinogenesis*

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Cancerigens (carcinogens, sarcogens, leukemogens) are the factors that cause cancer by initiating the cancerization process in normal cells. They differ from the factors that are essential for the maintenance and continuation of cancerous growth once it has become established. In fact, several of the best known cancerigenic agents, including some of experimental importance only, such as x-rays, radium, arsenic, benzol, urethane, stilbestrol and a few nitrogen mustards, display pronounced anticancerous properties, and some of them, because of these ambivalent properties, are used for therapeutic purposes. Cancer-producing agents thus are of practical and scientific importance for reasons of causation and prevention as well as of therapy. Although modern cancer research demonstrated carcinogenic properties for well over 200 chemicals including various metals and inorganic and organic compounds, the number of recognized or suspected endogenous and exogenous carcinogens that are responsible for the development of cancer in man is comparatively small. Moreover, many are not well defined chemical or physical entities but are mixtures of substances of more or less ill defined and often varying nature. However, the real and great significance of the few known or suspected human cancerigens lies in the fact that they provide the only definite clue to the causation of cancer in man and thus furnish the wedge by which, when properly applied, urgently needed information may be obtained on the etiology of the great majority of cancers of present unknown causation. The present discussion is confined to human cancerigens and cancerigenesis, cancerigens of experimental importance being mentioned only where they relate or may become important to the human problem.

CANCERIGENS

It seems appropriate to point out that all recognized human cancerigens are of exogenous, environmental nature and that the great majority of the suspected cancerigens are of the same type. This fact, it is believed, is not the result of mere coincidence but is of real significance. Contact with, and exposure to, these agents is associated with various activities and conditions, many of them closely related to the advent of the modern industrial environment. In fact, the bulk of known environmental cancer cases can be traced to exposure to certain occupational agents, while others are attributable to the usually improper use of certain medicines or medicinal devices, and to specific habits, customs, dietary imbalances, climatic and geologic conditions, parasitic infections and cosmetic agents. The value and extent of evidence supporting the cancerigenic properties varies a great deal with the individual factors.

The following summaries present the salient facts available concerning the known and suspected human cancerigens and their cancerous reaction products.

Organic Chemicals

1. *Anthracene Oil.* Crude anthracene oil is a product of the distillation of coal tar and is used in the manufacture of anthracene and grease, while anthracene oil residue is

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occasionally employed as a fuel. The active cancerigenic ingredient is not anthracene but an undetermined constituent of the oily portion. Cancers affecting the skin of the forearms, hands, face and scrotum following direct contact with the material were reported from Germany and England, while the occurrence of bladder cancer in a man who had handled anthracene residue for fuel purposes was recorded recently from Switzerland. The total number of anthracene oil cancers from all sources is about a dozen. The exposure time of the skin cancers ranges from seventeen to forty-two years and that of the bladder cancer was three years while its latent period was five years. The manifestation age of the patients with skin cancer ranged from thirty-three to seventy-two years. Chronic dermatitis, melanotic spots, atrophic areas and keratotic warts constitute the environmental cancer pattern that precedes and accompanies the development of the papillary and ulcerative carcinomatous lesions. So far only males have been involved. The hazard is entirely occupational. The incidence rate of skin cancer of the exposed worker population corresponds to three affected out of twenty-five to thirty workers. The experimental reproduction of this occupational cancer was successfully achieved in mice through skin applications of anthracene oil.

2. *Aromatic Amines.* Aromatic amino- and azo-compounds are obtained by the fractionation and processing of tar and are used extensively for the production of dyes, pharmaceuticals, photographic chemicals, antioxidants of rubber and flotation agents of ores. Of the great number and variety of these chemicals a few have exhibited cancerigenic properties in man while others have elicited such reactions in experimental animals. Of the human cancerigens of this nature, beta-naphthylamine and benzidine base have an established cancerigenicity to the urogenous organs, especially the bladder, while this is highly controversial for aniline which in American experience has not displayed any cancerigenic properties. The highly cancerigenic beta-naphthylamine, on the other hand, is active even when present as an impurity in presumably non-carcinogenic chemicals, such as alpha naphthylamine.

Among the aromatic amino- and azo-compounds, o-m-dimethyl-azo-benzol, benzidine, 2-amino-5-azotoluol, 2-acetylaminofluorene, n-ethyl-3:4:5:6-dibenzcarbazole, 4-dimethylaminoazobenzene-1-azonaphthalene, diazoaminobenzol, m-methyl-p-dimethylaminoazobenzene and several chemically closely related compounds have elicited cancers in internal organs, particularly the liver and bladder.

The total number of occupational bladder cancers caused by beta-naphthylamine, benzidine and possibly aniline and recorded among dye workers of Germany, Switzerland, Great Britain, Austria, Russia, Italy, Japan and France stands at present at well over 1,000. A few of these cancers involved the ureter or kidney. The route of exposure to these chemicals is by skin contact, inhalation and ingestion. The exposure time ranged from six months to forty years. The latent period which in most instances was equal to the exposure period was as short as two years and averaged from twelve to fifteen years. The manifestation age for the majority of the cancer cases was below fifty years and the rate of multiplicity was high. In several instances individuals in their third decade of life were involved. Telangiectases and hemorrhages of the bladder mucosa, leukoplakias, polyps and papillomas usually preceded the appearance of papillary or infiltrative and often multiple carcinomas. Because of the employment conditions existing in the dye industry, so far only male workers have exhibited bladder cancers due to exposure to the aromatic amines mentioned. The hazard is, according to existing knowledge, entirely an occupational one. In the past when the exposure was very severe, a condition not encountered any more in modern plants, 100 per cent of the exposed workers developed bladder cancers. The experimental reproduction of bladder cancers by feeding beta-naphthylamine to dogs was successfully

accomplished while similar procedures failed when benzidine was given which, however, elicited hepatomas, cancers of the eustachian tube and leukemia in rats.

3. *Benzol.* Benzol is a distillation product of tar and is employed for many purposes in a great number of industrial operations and products (rubber processing, printing, lithography, leather enameling, artificial leather making, rotogravure, rubber gasket can production, shoe manufacture, explosive production, paint remover, airplane dope, degreaser, bronzing pigment vehicle, rubber cement, dry cleaning fluid, impregnation of textiles with plastics, electroplating, buna rubber production, aromatic industrial chemicals and pharmaceuticals). While from an industrial hygiene aspect benzol is best known for its pronounced anemiogenic action, an appreciable number of more recent observations suggest that a prolonged and mild exposure to benzol may exert a leukemiogenic effect. The development of both myeloid and lymphoid leukemias as well as of lymphosarcomas has been charged to previous exposure to benzol. Reports on this subject have come from the United States, Italy, Germany, France, England and Belgium. The total number of cases recorded, however, is small (about fifteen). The route of exposure was by skin contact and inhalation. The exposure time ranged from three to ten years. The age of the individuals affected was from twenty to sixty years. The environmental cancer pattern found in these patients as well as among other workers simultaneously exposed to benzol showed the following manifestations: aplastic anemia, leukopenia, purpura, degeneration of the bone marrow (aplasiogenic effects) as well as erythrocytosis, leukocytosis, leukemoid reactions, hyperplasia of bone marrow, heterotopic myeloid foci and leukemoid proliferations in bone marrow and internal organs. The male-female ratio is 4 to 1. The type of exposure encountered was occupational. Attempts at experimental reproduction of benzol leukemia in mice yielded contradictory results.

4. *Chlorinated Hydrocarbons.* While occupational exposure to chlorinated hydrocarbons, especially those of aliphatic nature, have caused acute and chronic liver injury (acute yellow atrophy, cirrhosis) in man, no information exists as to a direct or indirect carcinogenic effect of these chemicals. Experiments on mice, on the other hand, demonstrated that prolonged administration of chloroform and carbon tetrachloride resulted in the development of hepatomas and carcinomas.

5. *Creosote Oil.* Creosote oil is a fractionation product of wood and coal tar and is used as a wood preservative, as a mold covering in brick and tile manufacture and as a disinfectant. Skin contact with creosote oil, especially when hot, has been followed by the development of cancer of the skin (hands, forearms, scrotum) in some fifty-five cases reported from England, Germany and France. The exposure time ranged from fifteen to forty years and the manifestation age was from fifty-one to seventy years. The appearance of cancerous lesions was preceded and accompanied by chronic dermatitis, hyperkeratoses, warts and papillomas. Multiple cancers were present in about 12 per cent of the cases. The hazard was entirely an occupational one. Skin cancers were produced in mice painted with creosote oil.

6. *Estrogens.* It has been possible to produce breast cancers with both synthetic and natural estrogenic substances in mice and rats, papillomas of the bladder in mice and rabbits and leukemias and testicular tumors in mice. Medicinal and occupational exposure of humans of both sexes has resulted in gynecomastia. There are some ten cases in which male patients treated for cancer of the prostate with large amounts of estrogens over prolonged periods of time developed unilateral or bilateral cancer of the breast. A causal relationship between the estrogenic medication and subsequent appearance of breast cancers in these patients appears likely.

7. *Petroleum and Petroleum Derivatives* (*Lubricating Oils, Fuel Oils, Tar, Pitch, Oil Black,*

Coke, Crude Paraffin Oil, Asphalt). The chemical composition of crude petroleums varies in different fields and even in different areas within the same field. Some crude petroleums contain considerable amounts of benzolic compounds while in others aliphatic-paraffinic constituents predominate. The chemical nature of crude petroleum derivatives obtained by fractionation and cracking (thermo-distillation, catalytic cracking under high pressure and temperature) depends in part on the chemical character of the crude product and in part on the cracking procedures used. Products obtained by the application of high temperature and pressure have a relatively high content of aromatic compounds because under such conditions aliphatic compounds are converted into aromatic compounds. Observations made on mice have shown that fractions obtained by the catalytic process that have a boiling point lower than 700°F. were apparently non-carcinogenic, while some products boiling above this temperature and known as bunker fuels displayed definite carcinogenic properties when painted on the skin of mice. Other experimental investigations demonstrated that some oils obtained by thermo-distillation and having a boiling point on both sides of the 700°F. point were carcinogenic. Human experience has shown that prolonged contact with crude paraffin oil such as that encountered by paraffin pressmen may cause cancer of the skin, particularly the scrotum. Other observations indicate that exposure to other heavy petroleum derivatives, such as fuel oils and lubricants, may be followed by cancer of the skin (hands, forearms). The total number of recorded petroleum oil cancers is relatively small (about 100). Contact with petroleum products is by skin contact, inhalation, ingestion and parenteral introduction (diesel jet injuries, lubricating gun injuries). The exposure time ranged from ten to sixty years and was, for the majority of cases, from twenty to forty years. The latent period after cessation of exposure was up to twenty years in some cases. The manifestation age was over fifty years in the majority of cases. Chronic dermatitis, comedones, boils, hyperkeratoses, warts and papillomas preceded and accompanied the appearance of these oil cancers which showed a multiplicity of 10 to 20 per cent. Males were mainly involved. The majority of the reported cases was of occupational origin, a few being of medicinal derivation. Skin cancers have been successfully reproduced in mice by the repeated application of various petroleum oils. Whether or not exposure to oil mists or ingestion of impure petroleum oils for various reasons (occupational, medicinal, dietary) can result in cancer of the lung or of the gastrointestinal tract is an open question.

8. *Shale Oil and Lignite Oils.* Shale oil is obtained by the retorting of oil shale which is found in many parts of the world. Shale oil production has been carried out for over seventy-five years in Scotland where the processed oils have been used extensively as lubricants in the textile plants, for some time and to a limited extent in Australia and for a few years in the United States. Crude shale oil stands chemically between crude petroleum oils and coal tar. In its carcinogenicity it also occupies an intermediate position, being less carcinogenic than gashouse tar and more carcinogenic than petroleum oils, generally speaking. Oil directly extracted by benzol from oil shale is non-carcinogenic and does not contain any benzpyrene. This chemical is found in the carcinogenic processed oils obtained by heating oil shale in retorts to temperatures of up to 1200 to 1400°F.

Oils of similar nature and industrial use are generated by the retorting of lignite (Germany). Both shale oils and lignite oils are used for the production of paraffin. Contact with the crude paraffin oil also has given rise to the development of skin cancer. In the paraffin workers as well as in the mulespinners of Great Britain the most prominent site of cancer was the scrotum. There are about 1,900 cases of shale oil and lignite oil cancer on record, the majority of which occurred among workers of the

British textile industry; a few cases were observed in the United States following the use of imported shale oil. Exposure to the oil is by skin contact, inhalation and ingestion. The exposure time for most cases ranged from thirty to fifty years for shale oil and from ten to thirty years for crude paraffin oil. The latent period was up to thirty years after cessation of exposure. The manifestation age during recent years was about sixty years. Hyperkeratoses, warts, comedones, boils, chronic dermatitis and papillomas usually preceded and accompanied the development of skin cancers which were multiple in about 15 per cent of the cases. While for a long time shale oil cancers affected males exclusively, the later employment of female mulespinners was followed by the appearance of skin cancers involving in part the vulva, a site corresponding to the scrotum which is the predominant localization of the male mulespinners' cancer. Shale oil cancer was reproduced successfully in mice but failed to develop when rabbits, guinea pigs and rats were used.

9. *Coal Tar, Pitch, Asphalt, Soot.* Tar, pitch, asphalt and soot are generated during the incomplete combustion of carbonaceous matter, such as coal, lignite, oil shale, petroleum, native asphalt, wood, vegetable matter (tobacco) and natural gas. The tarry matter present in all these materials and extractable from it by various organic solvents apparently contains carcinogenic substances responsible for cancers observed in man and experimental animals after prolonged exposure. The cancerigenic potency of the various products mentioned varies a great deal depending on the character of the source material and the methods of processing (temperature, oxygen supply) used, which in turn determine the relative amounts of tarry matter present and its chemical character. Thus different types of coal tars, for instance, display a remarkable variation in cancerigenic potency, gas-house and coke-oven tars usually being considered as most cancerigenic. Similar variations may exist in regard to the great number of domestic, industrial and commercial soots. While some of the soots contain appreciable amounts of tarry matter (chimney soot of fire places, lamp black), others have extremely small amounts (some of the carbon blacks). Products containing tars of various origin are produced and used extensively throughout industry (gas works, coke ovens, blast furnaces, steel plants, patent and packaged fuel manufacture, tar distilleries, chemical and paint manufacture, foundries, road construction, manufacture of tiles, linoleum, shingles, cables, insulation of electric appliances, corkstone, inks, rubber, roofing paper, water proofing of textiles, paper and masonry, cables, composition for optical glass grinding, and many others).

The occurrence of occupational and medicinal tar cancers mainly due to contact with coal tar, pitch or soot has been reported from many countries (Great Britain, United States, Germany, France, Italy, Belgium, Japan, Spain, Hungary, Switzerland, Russia, Austria, India, Holland). In fact, scrotal cancer in chimney sweeps was the first occupational cancer recognized (1775). Approximately 1,700 cases of tar and pitch cancer have been placed on record, the majority (1,500) of them being observed in Great Britain. This number, however, does not include the soot cancers found in sweeps. Exposure was by direct contact with the skin (dust, liquid) or by inhalation (dust, fumes) or by ingestion or by parenteral introduction (tar burns). Almost all of the recognized tar cancers in man were located in the skin and affected there the exposed parts (face, neck, hands, forearms) in addition to the scrotum. More recent evidence suggests that the inhalation of hot tar fumes such as encountered by stokers of coke retorts may cause cancer of the lung. Whether or not exposure to abnormally high amounts of atmospheric soot and to tar from excessive smoking of tobacco, especially cigarettes, carries a similar liability is still controversial but deserves serious consideration. Claims, moreover, have been advanced that occupational ex-

posure to tar was responsible for cancer of the oral cavity and bladder as well as for leukemia.

The average exposure time ranged from ten to twenty years although a few cases seemed to have developed after a contact of one to two years, especially in connection with tar burns. The latent period after cessation of exposure was as long as thirty years. The manifestation age varied a great deal and depended on the age at first contact as well as on the intensity of exposure and on the potency of the tar. Thus, scrotal cancer in chimney sweeps was found some hundred years ago even in boys in their teens who had entered this occupation when five to six years old. The majority of tar cancers of the skin in more recent times is found in persons between fifty and sixty years of age. Chronic dermatitis, melanosis, atrophic patches in the skin, warts, hyperkeratoses and papillomas compose the environmental cancer patterns of tar and pitch cancers. Multiplicity of cancers was observed in 20 per cent of the cases. The majority of cancers was found in males. The incidence rate among effectively exposed workers has run as high as 100 per cent after prolonged exposure to a potent tar (pitch workers with forty years of exposure or more). Tar cancers of the skin have been successfully reproduced in various species (mice, rabbits, rats, dogs) although other species have been refractory (monkeys). Cancers of various other internal organs (lungs, bladder, brain, connective tissue, stomach, bone marrow, uterus) have been elicited either by tar or by 3,4 benzpyrene, the cancerigen isolated from coal tar and soot.

Inorganic Chemicals

1. *Arsenic and Arsenicals.* Arsenic compounds are found in several metal ores (copper, zinc, silver, cobalt, lead) and are obtained as a by-product of the smelting of these ores. Arsenicals are used as pesticides, weed killers, wood preservatives, and in the manufacture of pharmaceuticals, glass, lead base alloys, dyestuffs, chemical warfare gases, sulfuric acid and many other products. Arsenicals may enter the general environment (air, water) from arsenicals released with smelter fumes, and from slag heaps of smelters or sprayed or dusted as pesticides on orchards, vineyards and cotton fields.

It is generally agreed that inorganic arsenicals may cause cancers of the skin when ingested, especially following prolonged medicinal administration. Occupational cutaneous exposure to arsenical dust is recognized by most but not all investigators as a carcinogenic hazard. Inhalation of arsenical fumes or dust, on the other hand, has been blamed for causing cancer of the lung in smelter workers and manufacturers of arsenical sheep dip. Claims have been made as to the causation of cancers of the upper alimentary tract following contact with arsenicals. Multiple epitheliomatosis of the skin was attributed to preceding parenteral administration of organic arsenicals (arsphenamines). The great majority of arsenic cancers were of medicinal origin (145 of 175) and affected the skin where they were situated on exposed and unexposed parts. Multiplicity of arsenic cancers was found in over 50 per cent of the cases. The exposure time of the medicinal cancers ranged from six weeks to many years while that of the occupational cancers ranged from four to forty-six years, with an average of about twenty-five years. The latent period of the medicinal cancers was from three to forty years (average eighteen years) while the exposure-free interval was up to eighteen years. The manifestation age of medicinal arsenic cancers was from twenty-five to seventy-five years and that of the occupational ones from thirty-five to sixty years. The environmental cancer pattern preceding and accompanying the cancerous manifestations was characterized by chronic dermatosis, melanoderma, leukoderma, hyperkeratoses, (palmar and plantar), warts and papillomas. Squamous cell carcinomas and basal cell cancers were found. The sex distribution for the medicinal cancers were three males

to one female while only males were involved in the occupational cases. The cancerigenic arsenic hazard was of occupational, medicinal and dietary-environmental nature. So far, no reliable experimental reproduction of arsenic cancers in animals has been accomplished.

2. *Asbestos.* Asbestos is a silicate containing calcium, magnesium, iron, nickel and/or copper. The chemical composition and physical characteristics vary with different types of asbestos which is mined in Canada, United States, South Africa, Russia, Chile and Cuba. Asbestos is extensively used in industry for the manufacture of insulation material, filters, brake lining, fireproof material (sheets, blankets, ropes, textiles, clinkers, mortar, paper, tiles, shingles) and gaskets.

Carcinogenicity of asbestos is not as yet definitely established. In view of the statistically excessive incidence of lung cancer among individuals affected by pulmonary asbestosis a causal connection between these two processes appears to be probable. A total of fifty cases of lung cancer co-existing with asbestosis has been reported from the United States, England and Germany. The incidence rate of lung cancer in persons with asbestosis that came to autopsy was between 13 and 15 per cent. The average manifestation age was around fifty years (range thirty-five to seventy-five years). The exposure time ranged from three to twenty-seven years (average fifteen years). The latent period after cessation of exposure was from ten to twelve years. Multiple lung cancers were found in several cases. The experimental reproduction of lung cancer in mice was reported.

3. *Beryllium and Beryllium Compounds.* Beryllium and its compounds are relative newcomers in the industrial field in which they have found widespread application (alloys, phosphors in fluorescent tubes, gas mantles, electric heating elements, atomic energy operations). Acute and chronic pulmonary reactions of inflammatory or granulomatous nature have been reported from the United States, England and Germany, and have occurred not only among workers in beryllium operations but also among persons residing in the immediate neighborhood of such plants. Since osteogenic sarcomas were produced in rabbits by the intravenous injection of several beryllium compounds, the possibility of future cancerous reactions in man deserves consideration.

4. *Chromium and Chromium Compounds.* Chromium and chromium compounds are obtained from chromite ores mined mainly in South Africa, New Caledonia, Philippine Islands and Turkey. Metallic chromium is used in various alloys (stainless steel, ferrochrome) for armor plates, high speed tools, gas turbines, jet motors and stainless steel sheeting. Chromite is employed in the manufacture of plastic cement and refractory brick, while chromic acid, chromates and other chromium compounds are used for electroplating pigments in paints, inks, ceramic glazes, rubber, linoleum, shingles, enamel, artificial marble, candles, crayons and for glass frosting.

An excessive incidence of lung cancer was observed among workers employed in German and American chromate plants where they were exposed to the inhalation of chromate dust. Recent German observations relate the occurrence of lung cancers to workers of chromium pigment factories (zinc chromate, lead chromate). There are at present more than 100 cases of lung cancer in chromium workers on record. The exposure time ranged from less than five years to forty-seven years with an average of fifteen years. The manifestation age was from twenty-nine to sixty-nine years. The latent period after cessation of exposure was more than five years. The environmental cancer pattern included chrome holes of the skin, eczema and perforated nasal septums. Nasal sinusitis is frequently present. Gastrointestinal disturbances, especially gastric ulcer, may have some significance. All individuals affected were males. The lung cancer death rate among exposed chromate workers is more than fifteen times that of the general

population. Experimental reproduction in animals of lung cancers following exposure to chromates has not yet been accomplished.

5. *Nickel and Nickel Compounds (Nickel Carbonyl).* Nickel-copper ores are mined mainly in Ontario, Canada, where they are in part processed, or they are sent to refineries in South Wales, Great Britain and in New York, New Jersey, Missouri and Washington. The Mond process involving the production of nickel carbonyl is used in most refineries. Nickel is employed for electroplating and in the manufacture of nickel steel, monel metal, German silver, nickel chrome alloys, nickel catalysts, coins, ceramics, pigments, storage batteries and enamels.

Cancers of the nasal sinuses and of the lungs have been reported among the workers employed in the British refineries. No similar observations have been made in Canada, the United States and Germany. The causation of the cancers of the respiratory tract among nickel refinery workers is still unsettled. While the bulk of the evidence incriminates nickel carbonyl vapors, it is held by some investigators that the inhalation of arsenic dust and fumes generated from impure sulfuric acid used in the refining process is the etiologic agent. Up to 1939 there was a total of thirty-four cancers of the nasal sinuses and twenty-four cancers of the lung on record from the British refineries. The hazard is one of inhalation and the involvement of the nasal sinuses in addition to the lung makes it likely that this is due to the inhalation of vapors and not of dust or fumes. The average latent period of the cancers was twenty-two years. Nasal polyps and papillomas often precede the development of sinus cancers. The hazard is entirely occupational, affecting males exclusively. An experimental reproduction of these cancers in animals has not yet been undertaken.

6. *Saltpeter-sodium Nitrate.* Cancer of the skin of the hands and feet was recorded among the workers employed in the nitrate fields of Northern Chile. Since the climate of these parts is very dry and sunny, it appears probable that not the chemical contact but excessive exposure to solar radiation represents the actual causative factor. A total of seventeen cases of cancer of the skin was placed on record. The exposure time was from twenty-eight to fifty years. The latent period after cessation of exposure was up to twenty-five years. The manifestation age ranged from thirty-seven to seventy-eight years. The environmental cancer pattern consisted of chronic dermatitis, dyskeratosis and papillomas. The hazard is an occupational one involving males exclusively. An experimental reproduction of these cancers in animals has not yet been attempted.

7. *Selenium and Selenium Compounds.* Selenium and selenium compounds have found considerable use in modern industry and are the cause of endemic selenosis among cattle in certain parts of the United States where the soil contains excessive amounts of this element. The evidence as to cancerigenic properties of selenium and its compounds is at present entirely of experimental nature. Rats fed selenium develop cirrhosis of the liver and hepatomas.

Physical Agents

1. *Radioactive Substances.* The number of radioactive chemicals originally belonging to the elements composing the uranium, actinium and thorium series has been increased considerably in recent years through the production of chemicals with synthetic radioactivity obtained by their exposure to ionizing radiation from a cyclotron or in a radioactive pile. Exposure to radioactive dust and gases may be sustained by working with radioactive ores such as pitchblende, carnotite and monazite sand or by consuming or bathing in the water of radioactive springs. Radioactive ores are mined in Czechoslovakia, Germany, Canada, the Belgian Congo and the United States. Radioactive substances are used for diagnostic and therapeutic medicinal purposes, and industrially in luminous paints, electrostatic eliminators, certain radio tubes, gas mantles, tracer substances and in the testing of welds and casts, in addition to the

development of atomic energy and atomic weapons. Radioactive substances emit ionizing radiation of particulate (alpha and beta rays) and /or electromagnetic (gamma) type rays. These radiations, which vary greatly in types, intensity and duration with the individual members of the three radioactive series, may elicit cancerous reactions in human tissues after excessive and usually prolonged exposure. The site of resulting cancers depends upon the type of exposure. Direct skin contact with the rays may cause carcinoma or sarcoma of the skin; ingestion of radioactive matter has been followed by the development of osteogenic sarcomas because certain radioactive metals are stored in the bones; sarcoma of the liver was reported many years after the intravenous injection of colloidal thorium dioxide (thorotrast) which is stored by the reticulo-endothelial cells. It is likely that the inhalation of radioactive dust and gases by the miners of the cobalt mines in Schneeberg and of the uranium mines in Joachimsthal is the cause of the highly excessive incidence of lung cancers among members of this occupational group. Suggestive evidence exists indicating that prolonged general exposure to radioactive radiation may be causally related to leukemia and lymphosarcoma.

The total number of the various types of radium cancers of occupational and medicinal origin is not large if one excludes the several hundred cases of lung cancers that have been seen in the miners of radioactive ores as well as all those cases in which a combined exposure to x-rays was present. There are not more than half a dozen radium cancers of the skin on record, some seven or eight osteogenic sarcomas in luminous dial painters, and perhaps a few leukemias among workers employed in radium concentration plants. The exposure time of osteogenic sarcomas was up to nine years while that of cancers of the lung ranged from thirteen to twenty-seven years, with an average of seventeen years. The manifestation age of bone sarcomas was between twenty and thirty-four years, of lung cancers between forty and seventy-five years, and only exceptionally as early as the middle twenties.

The environmental cancer pattern of radium cancers of the skin consists of chronic radiodermatitis with atrophies, telangiectases, melanotic spots, hyperkeratoses, loss of hair, loss of sweat and sebum secretion, papillomas and indolent ulcers. Osteogenic sarcomas are preceded by a chronic radio-osteitis, while leukemic reactions may be preceded by and /or associated with transitory anemia, leukopenia, lymphocytosis, degeneration of bone marrow, erythrocytosis, hyperleukocytosis, monocytosis, leukemoid reactions and hyperplasia of the bone marrow with maturation arrest. Multiplicity of cancers is most frequently observed with osteogenic sarcomas. The sex distribution of radium cancers followed closely the occupational conditions of employment. Osteogenic sarcomas occurred exclusively in females; cancers of the lungs, on the other hand, were observed in males only. Approximately reliable incidence figures of radium cancers among the total exposed worker-population are available only from the still somewhat controversial lung cancer group at Schneeberg where since 1876 between 70 and 80 per cent of all deceased miners died with cancer of the lung. The rate is said to be between 40 and 50 per cent for the Joachimsthal group. For comparison, it may be mentioned that the incidence rate of lung cancers among the general population stands at present at about 1 per cent of all deaths, but was less than $\frac{1}{10}$ of 1 per cent before the turn of the last century. Statistical studies of recent years yielded an excessive death rate from leukemia among radiologists and roentgenologists. Successful experimental reproduction of radium cancers in experimental animals has been accomplished for cancers of the skin, bone, lung and hematopoietic tissue.

2. *Roentgen-radiation or X-radiation.* Roentgen-radiation or x-radiation, which is generated by roentgen tubes, is used in industry for testing casts and welds, golf balls, molecular structures and crystalline

forms of chemicals. It is employed for fitting shoes in retail stores and for the removal of superfluous hair in cosmetic establishments. Its most widespread use is in medical and dental laboratories for diagnostic and therapeutic purposes. X-radiation, which is similar to gamma radiation, is cancerigenic. Roentgen-cancers, especially those of medicinal origin, have been reported from many countries. The total number of recorded occupational roentgen-cancers of the skin seen among radiologists, roentgen-technicians and nurses, roentgen-manufacturers and mechanics, and physicists, is about 150. Medicinal roentgen-cancers of the skin, joint tissues and bones have been recorded in appreciable numbers. The apparently excessive incidence of leukemia among roentgenologists has been attributed to prolonged exposure to weak penetrating radiation. Excessive exposure of the lungs for occupational or medicinal reasons, on the other hand, has not been followed by cancerous developments but by more or less severe and sometimes fatal fibrotic changes.

The exposure time varied greatly. Usually repeated exposures to roentgen-radiation, which sometimes extended over a period up to twenty-five years, were recorded. The latent period ranged from one to twelve years for skin cancers and from five to seventeen years for bone cancers after cessation of exposure. The manifestation age was between ten and eighty years. The environmental cancer pattern was identical with that described for the various cancerous manifestations caused by radioactive radiation. Multiplicity of skin cancers was reported in 30 per cent of the cases. Both males and females have been affected, the males predominating in the occupational group. Cancers of the skin, bone and hematopoietic tissue were produced in experimental animals by the administration of x-radiation.

3. *Solar Radiation and Ultraviolet Radiation.* Ultraviolet radiation, which is contained in the solar spectrum generated by various types of ultraviolet lamps and which occurs in the welding arc, possesses cancerigenic properties for the skin of man, mice and rats. It seems that this effect is limited to the mid-ultraviolet range covering 2700 to 3400 angstroms. Ultraviolet ray cancer of the human skin so far has resulted only from excessive and prolonged solar irradiation and mainly in individuals constitutionally predisposed, i.e., mainly blonde or red-haired, blue or grey-eyed and fair-complexioned, and often freckled individuals who show little or no tendency to tan and a pronounced tendency to burn when exposed to excessive amounts of solar radiation. Solar or ultraviolet-ray cancer of the skin is therefore unknown in negroes and in members of other dark-pigmented races.

Since the relative amounts of ultraviolet rays which inhabitants of dry and sunny climates or of regions of high altitude receive are especially high, solar cancer of the skin is particularly frequent among the outdoor workers of the midwestern and southwestern States and of the Rocky Mountain area (Colorado). Similar climatic conditions account for the high skin cancer incidence among the inhabitants of Australia and the Argentine. Intense ultraviolet irradiation is sustained by seafaring people (deck-hands, mainly). Cancer of the skin, especially the eyelids, has been observed also among the light-coated cattle in Texas, Australia and the highlands of Colombia.

Solar cancer affects the exposed parts of the skin, i.e., face, nose, eyelids, lower lip, neck, hands, forearms and feet. The exposure time is, as a rule, several decades unless a constitutional predisposition is present (xeroderma pigmentosum). The latent period is from ten to forty years and the manifestation age is from thirty to eighty years, the majority of cases being observed after fifty years. The environmental cancer pattern is characterized by the changes found in farmers' or sailors' skin, i.e., atrophies, dryness, scaliness, melanodermic spots, hyperkeratoses and papillomas. Multiplicity of cancers is frequent. Due to the predominance of males in outdoor activities, and because of the better protective care that women as a rule give their skin, solar

cancer is much more frequent in males than in females. Cancers (carcinomas and sarcomas) of the skin (ears, eyelids) have been produced in rats and mice exposed to the radiation emitted from ultraviolet lamps.

4. *Thermic Radiation.* The claim has been made that workers such as railroad engineers and steelmill workers who are exposed to intense radiating heat have an abnormal liability to develop cancers in the exposed skin which becomes chronically congested and inflamed. Apart from the fact that only a few cases of such an apparent origin have been reported, proper cognizance should be taken of the associated contact with tar fumes and soot usually present in occupations having the thermic hazard.

Such chronic thermic injuries must be distinguished, moreover, from those produced by acute burns which, when extensive and of third degree, may be followed after a prolonged latent period by the development of cancer in the scar. It is important to note that cancerous sequelae have not been observed after first or second degree burns but have appeared only when carbonization of the tissue was present. Cancers of the abdominal skin, not infrequently present among the shepherds of Cashmere and among Japanese who carry a metal or earthenware container filled with embers under their cloaks (kangri, kairo), exemplify this causative mechanism.

Miscellaneous Agents

1. *Parasites.* Of the many parasitic infections for which causal relations to subsequent cancerous reactions have been claimed, only infections with *Schistosoma hematobium* provide evidence of more or less definite nature. Recent investigators, however, have doubted the actuality of such a relationship connecting schistosomiasis of the bladder with subsequent development of cancer of this organ. While the bulk of the observations stem from Egypt where schistosomiasis is prevalent among the fellahs, similar evidence may appear in the future among American soldiers who contracted schistosomiasis during their war service in countries where this disease is endemic. Claims have been made, moreover, that schistosomiasis of the intestine and liver has been the cause of cancers in these organs. Schistosomiasis cancers of the bladder have a manifestation age of thirty to forty years and are present mainly in males.

2. *Tobacco.* In considering the question of potential cancerigenic properties of tobacco, a sharp distinction must be made between the action that may be exerted by extractives when cured and processed tobacco is chewed and that claimed for the various combustion and volatilization products when tobacco is smoked.

Numerous observations indicate that the habitual chewing of the betel nut quids consisting of a betel nut, powdered lime, tobacco and a buyo leaf, is related to the high incidence of cancer of the oral cavity among East Indians and Filipinos of both sexes. The causal agent in the quid is still controversial. Aromatic extractives of the buyo leaf, non-specific chemical irritation by the lime or by the tobacco extractives have been blamed for the cancerous effects. Since cancers of the lower lip and of the gum are prevalent among East Indians indulging in the khaini habit, where a quid of tobacco and lime is placed into the groove behind the lower lip, it is unlikely that the betel nut and the buyo leaf are responsible for the cancers of the mouth associated with the chewing of betal nut quids. It seems, therefore, that the number of potential cancerigens in the betel nut quid is narrowed to two substances, lime and tobacco. Recent observations made during World War II showed that the natives of New Guinea chewing a betel nut quid which does not contain tobacco do not suffer from cancer of the mouth. This holds true, also, for the Indians in the American Andes who chew quids of cocain leaves without the addition of tobacco and who apparently do not have an excessive incidence of oral cancer. From this circumstantial evidence it appears that extractives of cured and processed tobacco may be involved in the production of cancer

of the mouth. Because it is not likely that the tobacco of the orient is contaminated with arsenical insecticides, such as American-made tobacco frequently is, there is little probability that this chemical has any role in the production of betel nut cancer. Since the habit of chewing tobacco is not widespread in the United States, the question of the causation of oral cancer by tobacco extractives is of lesser importance here than that raised by the smoking habit.

An excessive smoking of tobacco (pipe, cigar, cigarette) has been related for quite some time to the development of cancer in the organs of the smoke tract (lip, tongue, cheek, oral cavity, larynx, bronchi and lung). However, the epidemiologic evidence advanced in support of such claims, although somewhat suggestive, has not been convincing while the experimental evidence has remained contradictory. Perhaps the best data supporting a causal connection between tobacco smoking and oral cancer come from certain parts of India where cancers of the mouth are frequent among inhabitants indulging in smoking cigars by the inverted method, i.e., with the lighted end in the mouth (chutta cancer), a habit apparently also practiced in Panama. However, under such conditions of exposure, contact of the oral mucosa with soot, fumes and tarry matter is much more direct than that of the ordinary method and is complicated by actual burns.

The epidemiologic evidence in regard to cancers of the respiratory tract due to the smoking habit is even less definite than that available for oral cancers. The possibility of such connections, however, remains an important problem deserving serious study. A causal relation between tobacco smoking and the recent increase in lung cancer incidence would be made much more probable if the surveys at present conducted on this question would show that heavy smokers (two or more packs of cigarettes a day) have a considerably higher lung cancer incidence than non-smokers of the same age and sex; that this reaction is most pronounced in persons who inhale the smoke and smoke their cigarettes until only a small stump is left; that there is a shift of the manifestation age of lung cancer in smokers toward a younger age group than that found in previous decades as typical for lung cancers, and seen among non-smokers; that the present male-female ratio of lung cancers (about 5:1) is shifted in favor of the female sex because of the in-increasing participation of women in the group of heavy smokers; and that the histologic type of cancers of the lung in women is shifted from a predominantly adenocarcinoma type to the squamous cell or anaplastic variety that prevails among males. Since the carcinogenicity of a tar tends to increase with the temperature at which the tar is produced and may also rise if the fumes are hot, it may be well to inquire into other details of the smoking habit, such as whether an individual is a fast or a slow smoker. Obviously, surveys of this type are necessarily very complex and may not readily yield unequivocal answers.

CANCERIGENESIS

The process of cancerigenesis is influenced not only by the potency of the cancerigen but also by various other factors which are responsible in part for the variations and fluctuations observed in the sex ratio, incidence rate, localization of cancer, length of latent period, manifestation age and primary multiplicity.

1. *Sex.* While a great deal of speculation has been expended on finding plausible explanations for the often striking differences in the incidence rate of certain cancers in the two sexes (respiratory cancers, bladder cancers, skin cancers), environmental cancers do not always follow these standards for obvious reasons. Most of the occupational cancers are found in males only because only male workers are employed in the hazardous operations (aromatic amine cancer of the bladder; chromate cancer of the lung; lung cancer in uranium ore miners, etc.). Whenever female workers enter the same operations, the respective

cancers occur also among them. For instance, shale oil cancer among textile workers was found originally in male mule-spinners only until female spinners entered the trade, when cancer of the skin, including the vulva, appeared among them. Cancer of the lung in workers with asbestosis was found not only in both male and female workers but there was also a shift of the sex ratio in favor of the females. Instead of a male-female ratio of 5:1, asbestosis cancer displays a ratio of about 2:1. Thus with equalization of the degree and duration of exposure to a cancerigenic agent there may follow an equalization of the sex ratio. A similar observation has been made in regard to the male-female sex ratio of oral cancer among East Indians chewing betel nut quids. While, as a rule, oral cancer is definitely more common in males than females, in certain parts of India this ratio is reversed. Likewise, factors that influence the degree of susceptibility to a carcinogen, such as skin pigmentation, may exert a similar influence on the sex ratio. While cancer of the skin in whites is highly predominant in males, the sex difference in the incidence rate of skin cancers is much less marked in Negroes.

2. *Incidence Rate.* Variations in incidence rates of environmental cancers depend on factors that are not always readily apparent and that have given rise to various misinterpretations. Incidence rates of environmental and especially occupational cancer exhibit a direct dependence on the intensity and duration of exposure to the cancerigenic agent. The intensity of exposure, in turn, is influenced by the relative potency of the particular cancerigenic agent. Without any doubt, marked differences exist in cancerigenic potency of various cancerigens, as well as of the same cancerigen when present in different physicochemical states and concentrations. For instance, compared with beta-naphthylamine gas-house tar appears to be a relatively weak carcinogen. This potency of tar is lessened when it occurs in a dilute form, such as soot, in which only a rather small portion is actually tar while the bulk is apparently non-carcinogenic carbon. A respiratory cancerigen, when present in the form of vapors and fumes, appears to be more active than the same agent when existing in the form of dust. If present in the form of dust the degree of exposure is, in turn, enhanced if the particles are below one micron size than if they are much larger, since the finer particles remain longer suspended in the air and penetrate deeper into the respiratory tract than do the larger particles. Likewise, contact with hot tar appears to elicit cancers more readily than does contact with cold tar.

The type of work done and working habits determine to a definite extent the intensity of exposure. Even when employed in the same operation some workers, because of the particular type of work they do, are bound to have a more intense and prolonged contact with the cancerigenic agents present than others, and for this reason exhibit a greater liability to development of the specific occupational cancer. For instance, workers engaged in strenuous physical labor requiring deep and frequent respiratory movements sustain a more severe inhalation hazard than do their fellow workers employed in light labor. Moreover, some persons are by habit dirty and careless, and thereby enhance their contact with hazardous material.

For sustaining an effective exposure to a carcinogenic agent it is not essential, on the other hand, that the contact be a continuous one. It may well be intermittent and, in fact, severe intermittent exposures may prove to be more effective in eliciting a cancerous response than is continued mild exposure. This relationship between type and interval of exposure and incidence rate of cancer is supported by the fact that in some cancerigenic operations the maintenance and repair workers having only discontinued but intense contacts are particularly liable to the development of occupational cancers.

From the information available on the influence of individual heredity upon the susceptibility to exogenous cancerigens, it

appears that heredity plays no significant role in this respect. Since exposures to occupational cancerigens are often relatively intense, the cancerigenic effect appears to be sufficiently severe to overcome any minor hereditary differences in reactivity that might be present. Experiences in occupational cancerigenesis demonstrate that, given a potent cancerigenic agent and an exposure of sufficient intensity and duration, there are no appreciable differences in susceptibility noticeable among the exposed workers if due consideration is given the various factors mentioned that modify the degree of individual exposure. Racial characteristics, on the other hand, definitely control the susceptibility to certain types of cancerigens, such as ultraviolet radiation and cancerigenic oils and tars. It is common experience that Negroes display a remarkable, while not absolute, degree of resistance to cancerigenic oils and tars. Whether the same holds true as to the action of solar rays remains to be determined, since Negroes in the tropics are apt to develop cancers in ulcers of the lower leg where the normal protective epidermal covering has become defective and solar rays can act on unprotected proliferating epithelium.

Important in determining incidence rates of environmental cancers is the age at onset of exposure and the intensity of exposure. Clinical and experimental evidence has shown that the length of latent period depends in part on the intensity of exposure, i.e., the more intense the exposure, the shorter the latent period. However, the reduction of the length of the latent period is subject to definite limitations since it apparently cannot be decreased below a certain minimum. On the other hand, if the intensity of exposure is very mild or the cancerigenic agent is only weakly potent, it is likely that the latent period will be correspondingly very long, and cancers from such exposures are apt to appear at a late period of life. A similar effect is produced if the age at onset of exposure is shifted into the more advanced periods of life. Cancers under such conditions are likely to occur during the senescence period, or the average manifestation age may lie even beyond the average life span.

The various considerations mentioned that determine incidence rates of environmental and especially occupational cancers are of definite importance in epidemiologic and statistical studies. While it is permissible and justifiable to calculate incidence figures on lung cancers for the entire present and former worker population of chromate plants, since all workers of such plants are exposed to the inhalation of chromate dust, the same procedure applied to dye workers for determining the incidence rate of bladder cancers due to aromatic amines is highly misleading, because only that relatively small group employed in the manufacture of the dye intermediates, alpha- and beta-naphthylamine and benzidine have appreciable contact with these cancerigens unless production of these chemicals is carried out under improper technical and sanitary conditons.

It appears, moreover, that the younger the average manifestation age of a certain occupational cancer, the better are the chances of determining the actual scope of a hazard and the more complete the incidence figures tend to be. On the other hand, the older the average manifestation age of an occupational tumor, the greater is the probability and possibility that effectively exposed individuals may die from other causes than occupational cancer.

3. *Site of Cancer.* The site of environmental cancers is dependent, in part, on the type of exposure and in part on the physicochemical properties of the cancerigenic agent. Direct skin contact, for example, results in most instances in the development of cancer of the skin (tar, soot, pitch, petroleum products, solar rays, roentgen-radiation, etc.). The same location, however, may result if the cancerigenic agents, such as arsenicals, are stored in the skin after having entered the body through other routes (ingestion, inhalation). Direct primary contact, also, accounts for the cancers of the respiratory system (lung, nasal sinuses) due

to the inhalation of cancerigenic vapors, gases, fumes or dust (tar, chromates, arsenic, nickel carbonyl, asbestos and radioactive minerals). The cancer of the bladder of dye workers is caused by an excretory mechanism since the aromatic cancerigens are excreted with the urine and reach the bladder where they come in contact with the bladder mucosa over a longer period of time than with any other part of the urogenous tract. A depository mechanism again is active in the production of osteogenic sarcomas after the ingestion of radioactive material and in the development of leukemia after exposure to benzol, since radium is deposited in the bony substance while benzol is retained in the fat cells of the bone marrow. The osteogenic sarcomas following repeated medicinal irradiation with roentgen-rays, on the other hand, are reactions to direct primary contact with the cancerigenic agent.

4. *Multiplicity.* An excessive primary multiplicity of cancers is characteristic of many occupational reactions, such as bladder cancers in dye workers, arsenic cancer of the skin (both occupational and medicinal); roentgen-cancers of the skin; tar, pitch and oil cancers of the skin; and radium sarcomas of the bone. Occasionally, multiple synchronous or heterochronous cancers may affect different organ systems such as skin, stomach and lung in paraffin oil workers; skin and lung or upper digestive tract in arsenic workers; and skin and bladder in tar workers. It is likely that such multicentric responses to cancerigenic agents reflect, to some degree, the intensity of exposure. In part, they may be the result of simultaneous contact through various routes, which occurs not infrequently under various occupational conditions.

CONCLUDING REMARKS

It is hoped that this brief panoramic view of the types and properties of exogenous cancerigenic agents directly significant to the human problem may aid in stimulating increased interest and understanding of this important yet little cultivated field of the general cancer problem. A sympathetic and understanding attitude of all people concerned with environmental cancer hazards toward their more comprehensive investigation should help a great deal in unravelling the many still unsolved problems of cancer causation and in aiding in the final conquest and control of this serious threat to human health and happiness.

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Conference on Therapy

Household Poisonings II

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. HARRY GOLD: In the conference today it has been planned to extend the discussion of household poisonings with a view to exploring more fully the details of treatment. Several of the more common household accidental poisonings were taken up in the previous conference[1] and attention was directed chiefly to the circumstances under which these problems arise in the home. A noteworthy feature of the comments was the emphasis placed on the desirability of skillful temporizing and the avoidance of overtreatment, since so very often not enough of the poison has been swallowed to do any harm and quite frequently the real trouble arises as the result of attempts at treatment. The fact remains, however, that many cases of accidental household poisoning do result in disasters some of which may be avoided by the appropriate use of both general and specific therapeutic measures.

In the previous conference on this subject, Dr. Helpern mentioned arsenic as the most common source of danger in rat poisons. Dr. Modell, you had an experience with a case of poisoning by a rodenticide a few days ago. Tell us about it.

DR. WALTER MODELL: One of our recent graduates, an intern in a nearby hospital, telephoned to me about midnight and related that a two year old child swallowed some of the material which a rat exterminator had left in a cup in the cellar. He described it as brownish and mushy. There were no symptoms. He had washed the stomach about forty-five minutes after the material was taken. The exterminator could not be reached and, under the circumstances, the best one could do was to hazard a guess as to the nature of the poison. "Rough on Rats" is stated to contain 56 per cent metallic arsenic and 20 per cent barium carbonate but this makes a slate-colored powder. Strychnine is often used as a rat poison but this usually comes in seeds. There are several pastes on the market which are used as roach and rodent poisons and which contain from about 1 to 2 per cent yellow phosphorus. The characteristic odor may sometimes serve to identify these materials but had not been noted in this case. Red squill, an effective rodenticide, is often supplied in brownish cakes or biscuits which, after soaking in water, may become a brownish mushy mass and this seemed to fit the description of the material taken by the child. In this event the danger would not be great because red squill is very poorly absorbed by humans and it is highly emetic. While any of the poisons might be mixed with material to give it a brown mushy appearance, red squill seemed to be the most reasonable guess. It turned out to be wrong. Circulatory collapse developed in about five hours and the child died in about twelve hours. It was learned that the compound was sodium fluoracetate (1080) which the exterminator had used in violation of the law. This compound is a violent poison which causes death with convulsions and ventricular fibrillation in a dose of about 5 mg. per kg. There are no known antidotes or effective treatment.

Incidentally, while we are on the subject of rat poisons I might mention alpha-

[1] Conference on Therapy. Household poisonings. *Am. J. Med.*, 6: 139, 1949.

naphthyl thiourea, also known as ANTU, a recent development in the field of rat poisons which we are likely to encounter from time to time. It is a very interesting poison producing pulmonary edema by an action on the pulmonary capillaries. While it is extremely toxic to the rat, it is relatively innocuous in some species of animals. On the basis of experience with the monkey the lethal dose in man is stated to be of the order of 4 gm. per kg. A man might consume a pound or more of the 20 per cent preparations on the market without serious effects.

DR. GOLD: I should like to say a few words about the cigarette as an item in household poisoning. Babies sometimes eat cigarettes. I have in my file an account of such a case. The mother discovered that her one year old baby had eaten two cigarettes. She administered milk and the baby promptly vomited the milk together with about one-fourth of the tobacco. What remained represented about 45 mg. nicotine, or approximately 4 times the lethal dose for a 10 kg. infant. When the doctor arrived about three hours later, the baby seemed weak and listless. He administered syrup of ipecac but this failed to produce vomiting. He was advised to wash the stomach with a 1:10,000 solution of potassium permanganate and to leave a few ounces of the solution in the stomach. This was promptly carried out and no further signs of nicotine poisoning developed. It is difficult to be certain whether these measures played any part in the uneventful recovery. Administration of potassium permanganate was a rational procedure because nicotine is very rapidly destroyed by this oxidizing agent. Little is known of the hazard of nicotine poisoning when cigarettes are eaten. The alkaloid, nicotine, is a violent poison and is absorbed from mucous membranes within a few minutes. A cigarette contains about 30 mg. of nicotine and the fatal dose of nicotine for a man is of the order of 60 mg., the content of about two cigarettes. It seems, however, that nicotine is not nearly as serious a danger when taken by mouth in the form of cigarettes. We administered enormous doses of cigarette tobacco by stomach tube to cats, doses as high as 2 gm. per kg., which represented as much as approximately 60 mg. of nicotine per kg., or about 6 times the lethal dose for cats. Symptoms appeared very quickly; within a few minutes the animal showed twitching of the ears, then nausea, and within fifteen minutes or less there was vomiting with expulsion of the tobacco. That was all there was to it; within a few hours all ten animals were well. In two additional animals morphine was given to prevent vomiting and these died of nicotine poisoning. Apparently, absorption of nicotine from tobacco taken by mouth is markedly delayed, and there is indication from experiments in animals that nicotine is less than one-fifth as toxic when taken in the form of tobacco. The fairly prompt vomiting induced by the absorption of the initial fraction is, of course, a factor of safety.

In recent years a few highly effective and specific antidotes to some poisons have been developed. Dr. Riker, would you say a few words about the specific treatment of poisoning by arsenic?

DR. WALTER F. RIKER: BAL, or 2,3-dimercaptopropanol, is a specific antidote to poisoning by arsenic. The details of its actions were discussed in the therapy conference on BAL which was published in Volume III of the Cornell Conferences on Therapy. A few significant points might be mentioned here. This material is now Council Accepted and is available in the form of a 10 per cent solution in peanut oil in ampuls containing 4.5 cc. The sulfhydril groups in BAL compete with the sulfhydril groups of tissue enzyme systems for the arsenic, and in that way the tissues are protected against arsenic. BAL has such a strong affinity for arsenic that it may even remove the metal from combination with protoplasm. This is an important aspect of its use as an antidote if tissue damage has not progressed too far. BAL exerts its protective action by increasing the excretion

of arsenic in the urine and also by the fact of the conversion of arsenic into a dithioarsenite which is relatively non-toxic. Most of the experimental and clinical experience relates to the treatment of poisoning by therapeutic arsenicals such as mapharsen. In such cases, doses of the order of 5 mg. per kg., or about 300 mg. (3 cc. of the 10 per cent solution), may be given intramuscularly every three or four hours as long as seems to be indicated by the evidence of arsenic poisoning. BAL has toxicity in its own right, causing lacrimation, blepharospasm, vomiting, unrest, paresthesias and muscular cramps. When these symptoms occur, the administration of BAL has to be interrupted, or the doses reduced, or the intervals prolonged. A noteworthy feature is the fact that BAL is rapidly excreted and toxic symptoms occurring after such doses as I have stated are apt to subside within a few hours.

DR. GOLD: While the experimental proof is strong that BAL enables animals to recover from otherwise fatal doses of arsenic, how about the evidence in man? Have any human lives been saved?

DR. RIKER: I have no doubt of it. There are now numerous favorable reports in the literature and the evidence for the value of BAL in reversing toxic effects of arsenic is quite convincing.

STUDENT: Do the results with BAL in the case of mapharsen apply to inorganic arsenic?

DR. RIKER: Yes, they do.

DR. GOLD: How about potassium arsenite? Fowler's solution might join the list of household poisons since a good deal of use is made of it as a so-called "tonic."

DR. RIKER: BAL proved effective in our animal experiments in poisoning by Fowler's solution.

DR. GOLD: How about the use of BAL by oral administration against oral arsenic, since that is the form a case of household poisoning is apt to take?

DR. RIKER: There is no published experience on this point but I can see no reason why BAL should not be given by mouth or introduced into the fluid used in washing the stomach. It would precipitate the arsenic, if taken in a soluble form, and leave the insoluble and poorly absorbable thioarsenite in its place. Metallic arsenic might also be converted into the relatively innocuous thioarsenite and in this way protect the mucous membranes against the local action of the arsenic.

DR. MODELL: Dr. Gold, how much BAL would you think one might give a patient when there is reason to believe that the arsenic is still in the gastrointestinal tract?

DR. GOLD: BAL is a toxic substance and there is some indication that its potency by oral administration may not be much lower than by intramuscular injection, although the evidence on this point is not entirely satisfactory. As to the specific answer to your question, there is no experience in this matter. One might hazard a guess on the basis of the fact that BAL combines with arsenic in equi-molecular proportions. Accordingly, 250 mg. of BAL would combine with approximately 150 mg. of arsenic, or in a ratio of about 2:1. Since, for example, "Rough on Rats" contains about 50 per cent arsenic, an oral dose of 0.25 gm. of BAL would be expected to afford protection against approximately 0.25 gm. of this rat poison, the latter representing about twice the smallest dose of arsenic said to be fatal in man. Little if any toxicity from this dose of BAL would be expected since the arsenic, by its combination with BAL, also serves as an antidote to the BAL. In actual practice the utility of BAL as an oral antidote might be much greater than indicated by these figures because larger doses of BAL could be used in situations in which it is likely to be removed by stomach washings.

DR. MODELL: How would one prepare the fluid for lavage since BAL is supplied as a solution in oil?

DR. GOLD: How about that, Dr. Riker?

DR. RIKER: BAL is soluble in water up to about 2 per cent. One could simply shake up the oily solution with water.

DR. GOLD: Dr. Modell, would you say a few words about poisoning by bichloride of

mercury and lead? Corrosive sublimate is not so frequent a form of household poisoning as it used to be but there are occasional accidents and attempted suicide with this compound is still encountered. Also, do babies still poison themselves by eating the paint on their cribs or toys?

DR. MODELL: We do not see so much bichloride of mercury poisoning at the present time. I suppose the fact that this drug is now sometimes put up in tablets resembling a coffin and colored blue has something to do with it. There is also the fact that many less dangerous materials for antiseptic washes have become more popular. The condition, however, is far from rare. Longcope and his associates assembled forty-two cases in a period of about a year in Baltimore in connection with their study on BAL which was published in the July, 1946, issue of the Journal of Clinical Investigation. Past experience left one in some doubt that any antidote or method of treatment would prove successful in poisoning by mercuric chloride because of the extraordinary speed with which this compound produces irreversible damage in the gastrointestinal tract, locally, and in the kidneys. Dr. Gold, you recall the case we had here in the hospital several years ago, at the time we were studying sodium formaldehyde sulfoxalate which had been proposed as an antidote. This compound offered considerable promise because it was relatively innocuous and could be given in large amounts by mouth and by vein. It promptly precipitated the mercury which was in the gastrointestinal tract and in the bloodstream, and the precipitate was much less toxic. This was an eighteen year old girl who swallowed 1 gm. of bichloride of mercury in a half glass of water. She vomited almost immediately. Active treatment was started in the hospital about thirty minutes after the drug was swallowed. She received abundant washing of the stomach, colonic irrigations, intravenous infusions of sodium formaldehyde sulfoxalate, and gastrointestinal washings and irrigations with the same compound. The whole situation seemed to have been most favorable for protection by the new antidote, in fact, most favorable for recovery even without an antidote. In spite of it all, poisoning progressed and in two weeks she died of uremia. The use of BAL has created a most dramatic change in the outlook for patients poisoned by mercuric chloride. The experience of Longcope and his associates shows that recovery is now assured after even 1 gm. or more taken several hours previously with the proper use of BAL as an antidote. Some of their cases were in a desperate state of poisoning at the time that therapy was started. With rare exceptions, recovery was complete in a matter of several days to three weeks. In one case the dose of poison was enormous, 20 gm.; in another case the delay in starting the treatment was very long (nineteen hours). There is evidence that mercury poisons the tissues by a mechanism similar to that of arsenic. There is also fairly strong evidence that BAL can withdraw mercury from its combination with tissue proteins and in that way reverse damage. There has been no experience, as far as I know, with the use of BAL for stomach lavage in the case of bichloride of mercury poisoning. There can be no doubt of the wisdom of emptying and washing the stomach at the earliest possible moment even though such a potent systemic antidote is available. The most favorable schedule for the use of BAL in poisoning by bichloride of mercury is similar to that already described in the case of arsenic poisoning, 5 mg. per kg. intramuscularly, every three or four hours for as long as seems indicated. The dose may have to be reduced as symptoms of BAL poisoning appear in an individual unduly sensitive to it.

In regard to lead poisoning, Dr. Gold, you asked whether children still are poisoned by eating the paint off their cribs and toys. That source of danger has been greatly reduced because these items are now quite generally covered with paint which does not contain lead; although when the father repaints them, he may use paint

containing lead pigments. Poisoning with lead is still encountered in infants and children who eat the paint off the veranda or woodwork in the house. In the previous conference, Dr. Dale mentioned this source of poisoning in the few cases that have been seen in the Pediatrics Department of the New York Hospital.

Most cases of lead poisoning are of the chronic variety, whether in children or in adults. The recognition of lead poisoning is not easy. The symptoms develop insidiously and resemble many other diseases. There is impairment of the appetite, constipation, vomiting, abdominal cramps and a moderate degree of anemia. Basophilic stippling of the red cells sometimes points in the proper direction but this is not confined to lead poisoning and it may be absent even in severe cases. In children, a broad line of density at the growing end of the long bones seen in the x-ray is a very helpful sign when it is characteristic, although narrower lines of density of the same general character are present in other conditions. Children are said to be more sensitive than adults to lead encephalitis, and in general to lead poisoning. The encephalitis gives rise to mental changes, optic atrophy with blindness, projectile vomiting, stupor and convulsions. It appears to be associated with increased intracranial pressure due to edema of the brain. The finding of lead in the urine, feces and blood does not always decide the diagnosis because there is some lead in the tissues of normal people as the result of the lead intake in the daily diet, which contains about 0.25 mg. Most of this is found in the feces (about 0.2 mg.) and about one-tenth as much in the urine. The normal blood may contain about 0.05 mg. per 100 cc. In high exposures the lead content may rise to 10 times the normal or more, and the finding of such quantities as 0.2 mg. per L. in the urine helps interpret the cause of symptoms and physical signs in the patient.

The treatment of lead poisoning is not in a satisfactory state. While BAL has produced striking results in the case of some metals, its use in lead poisoning has been disappointing. It seems that the best results are obtained in cases that are recognized early and in which the source of further poisoning is removed. In the course of time enough of the lead is excreted to insure complete recovery. In the presence of active symptoms of lead poisoning the chief treatment consists of large amounts of calcium, in addition to measures which promote calcium absorption and calcium deposition in the bones. The rationale is based on the view that the insoluble form of calcium in bone is not harmful, and the further observation that lead in the blood and soft tissues follows the course of calcium with respect to deposition in the bone. Milk is made the chief item of diet. It contains about 1 gm. of calcium per quart. Calcium phosphate in doses of 1 to 2 gm. three times daily may be given as a form of calcium readily deposited in bone. Vitamin D in the form of the U.S.P. preparation of synthetic oleovitamin D (containing 10,000 or more units per gm.) may be given in doses of 1 or 2 cc. three times daily. Abdominal cramps may be controlled by the intravenous injection of a 5 per cent solution of calcium chloride in total doses of from 5 to 20 cc., injected slowly at the rate of about 2 cc. per minute. Such treatment is apt to bring many of the acute symptoms under control within a few days. Sodium citrate in oral doses of 1 to 2 gm. three times daily in children, and 2 to 4 gm. in adults, has been reported to cause fairly prompt relief of symptoms associated with a fall in the lead concentration in the blood and an increase of lead excretion in the urine, presumably as the result of conversion of tertiary lead phosphates into a soluble complex which is not readily dissociated.

The patients in whom the measures which I have just described have brought about relief of symptoms still remain in danger of recurrence of symptoms under conditions which promote the release of lead from the bones, such as diets which are low in calcium, diets which promote alkalinization or acidification of the tissues,

and metabolic disturbances in acute infections. In connection with this problem practices differ. There are those who prefer to continue the program which locks the lead in the bone, those who allow the patient to "delead" himself gradually and those who take active measures to "delead" when the patient is in an optimum state of health. "Deleading" involves the risk of producing acute symptoms of lead poisoning in consequence of the transfer of lead from the bones to the blood, brain and other tissues. There are several measures which promote this process, namely, low-calcium and high-phosphorus diets, systemic acidification and parathyroid hormone. In such cases the patient may receive a diet which contains little or no milk and no vegetables or fruit. The diet consists mainly of meats, fats and cereals. Ammonium chloride in doses of about 5 to 8 gm. daily helps to shift the acid-base equilibrium toward the acid side. Parathyroid hormone may be given in doses of 100 units once or twice a day intramuscularly to promote the mobilization of lead from bone (which follows the course of calcium) and to promote its excretion in the urine. Various methods for "deleading" differ in details but they are essentially similar in principle to the measures I have described. "Deleading" is best carried out in a hospital.

On the whole, the results of treatment in lead encephalitis are not very satisfactory. Hypertonic solutions of glucose may help temporarily to control symptoms due to high intracranial pressure. Spinal tap to lower pressure may be of some value. Permanent injury of the brain as the result of high intracranial pressure is common in survivors of lead encephalitis.

DR. GOLD: Accidental cyanide poisoning in the home is a very rare occurrence in these days but there are about twenty-five hydrocyanic acid and cyanide deaths a year in New York City involving industry, fumigation, homicides, suicides and other means of exposure to this violent poison. Seeds of various fruits—apple, peach, plum, cherry—may cause poisoning and there was a report of human poisoning from the eating of chokecherry seeds a few years ago. I recall an experience with one of the persons in the department of chemistry several years ago. She was drawing up cyanide solution in a pipette and some of it came up into her mouth. She promptly spat and rinsed her mouth thoroughly. She thought the danger under the circumstances was negligible but she could not dismiss it altogether. About thirty minutes later she began to feel faint and giddy and ran upstairs to our laboratory for advice. She was pale and her pulse was rapid. There was no satisfactory treatment at that time and since about forty-five minutes had elapsed without progression of symptoms she was assured that the danger was negligible. Her symptoms improved quite promptly. I am inclined to think it was a case of panic. Had this occurred today I might have turned to more certain antidotes. Dr. Cattell, would you say a few words about the present treatment of cyanide poisoning?

DR. MCKEEN CATTELL: It has long been known that methylene blue, the nitrites and sodium thiosulfate or "hypo" are effective in cyanide poisoning. The more recent experiments of Chen and his collaborators have resulted in a plan of treatment in which both nitrites and thiosulfate are used in such a manner that dogs recover from as much as about 20 times the fatal dose of cyanide. Either drug alone protected against only about five fatal doses of cyanide. They suggested the intravenous injection of 0.3 gm. sodium nitrite (10 cc. of a 3 per cent solution) in a period of two to four minutes. This is to be followed promptly by an intravenous dose of 12.5 gm. of sodium thiosulfate (50 cc. of a 25 per cent solution) injected over a period of about five to ten minutes. It is recommended that one-half the dose of the two drugs be repeated in about two hours and that the patients be kept under observation for twenty-four hours or longer for the possible need of further treatment.

VISITOR: Is there time enough to get such

treatment going in the case of cyanide poisoning as it occurs in humans?

DR. GOLD: One has to anticipate such poisonings and make some preparation for them. Chen and his collaborators suggested a small kit containing 2 ampuls of 10 cc. each of 3 per cent sodium nitrite, 2 ampuls of 50 cc. each of 25 per cent sodium thiosulfate, and a sterile 10 and 50 cc. syringe with needles. It is also to contain 12 pearls of amyl nitrite. The patient may be given amyl nitrite by inhalation as an antidote to tide over the period required for the preparation of the solutions. Neosynephrine or paredrine may be given in 5 or 10 mg. doses by intramuscular or intravenous injection to counteract the vasodepression caused by the nitrite.

There is no doubt of the need for speed in cases of human cyanide poisoning. Symptoms occur in rapid succession, giddiness, faintness, vomiting, respiratory stimulation followed by depression, coma and convulsions. Only thirty minutes may elapse before the respiration stops but in some cases a period of two to three hours may be available for the application of antidotes. There are chances for recovery as long as the heart beats, and additional time is gained by artificial respiration in the event that breathing has ceased. There are now records of many cases of cyanide poisoning in humans in which these antidotes have proved effective. The effects are dramatic; poisoning in which there was coma and profound respiratory depression has been reversed in a few minutes after the injection of the antidotes.

STUDENT: Cyanosis is often mentioned as a symptom in cyanide poisoning. I was wondering about that since cyanide is supposed to poison the respiratory catalysts so that tissues cannot take oxygen out of hemoglobin and venous blood remains brighter red than normally.

DR. GOLD: That is correct, and at the onset of poisoning the patient is not cyanotic. He becomes so only late in poisoning when there is profound respiratory and circulatory failure.

STUDENT: No mention has been made of vomiting or gastric lavage in the treatment of cyanide poisoning. Is it absorbed so fast that this measure is of no importance?

DR. GOLD: Prompt emptying of the stomach is important; also lavage with an oxidizing agent like solution of hydrogen peroxide diluted 10 times, or 1:10,000 solution of potassium permanganate. If the patient is in coma, it may be impossible to produce vomiting; also, vomiting and washing the stomach in such patients carry the danger of aspiration pneumonia.

DR. JANET TRAVELL: Perhaps it is unnecessary to state that apomorphine should not be used in comatose patients. Yet I saw a patient who had taken lysol and had become comatose to whom apomorphine was given to induce vomiting. Emesis did not take place and within three or four minutes a very profound respiratory depression ensued which necessitated the use of carbon dioxide and oxygen. Apomorphine often fails to cause emesis in comatose patients.

DR. CATTELL: It is a known fact that during coma apomorphine markedly depresses the respiratory center.

STUDENT: How do the antidotes to cyanide work?

DR. GOLD: Dr. Bodansky, you experimented on the problem of cyanide poisoning during the war. Will you tell us something about the mechanism of action of the antidotes and also about your experiences?

DR. OSCAR BODANSKY: The treatment recommended by Dr. Chen rests chiefly on experiments in which the effect of amyl nitrite inhalation or of the intravenous injection of sodium nitrite, accompanied in either case by the intravenous injection of sodium thiosulfate, was determined in animals receiving sodium cyanide by subcutaneous injection. In such cases there is an opportunity for methemoglobin to form from the action of the nitrite while the cyanide is being absorbed into the circulation. The conditions here are similar to those in poisoning by oral ingestion of cyanide. The methemoglobin and thio-

sulfate greet, as it were, the entering cyanide and detoxify it. The methemoglobin does so by forming cyanmethemoglobin, and the thiosulfate by forming thiocyanate.

We were faced with a somewhat different problem in our investigations during the war. In poisoning by inhalation the hydrocyanic acid or cyanogen chloride enters the circulation very rapidly and a lethal amount may paralyze tissue respiration before therapy can be instituted. We wanted to know whether an already established lethal degree of cyanide poisoning could be reversed by the rapid induction of methemoglobinemia. In poisoning under the circumstances we were considering the inhalation of a lethal dose might occur very rapidly, indeed within a few seconds, and death might follow within a few minutes so that the application of intravenous therapy might be impractical. We therefore tried to determine how effective prompt induction of methemoglobinemia by the inhalation of amyl nitrite would be under these conditions and, further, to what extent the prophylactic induction of methemoglobinemia would be effective in counteracting the result of anticipated exposure to a lethal dose of hydrocyanic acid or cyanogen chloride.

We exposed a number of dogs in pair to an approximately lethal dose of hydrocyanic acid in a gas chamber. One dog in each pair was given artificial respiration and treated with amyl nitrite about a half minute after removal from the chamber, while its partner served as a control receiving only artificial respiration. It was found that amyl nitrite exerted a significant therapeutic effect when cyanogen chloride was the toxic agent but not in the case of hydrocyanic acid. On the whole, treatment after exposure to a lethal dose by inhalation proved unsatisfactory and so we turned to the problem of prophylaxis. We induced methemoglobinemia in a number of dogs by oral or intramuscular administration of PAPP (p-aminopropiophenone). The results were very striking. The dose of hydrocyanic acid tolerated by methemoglobinemic dogs proved to be, in general, proportional to the degree of methemoglobinemia. The latter protected against 2 to 8 times the dose of cyanide which would be lethal to over 90 per cent of unprotected animals. One dog in which a 49 per cent methemoglobinemia had been induced withstood an exposure about 40 times the dose lethal to unprotected animals. We obtained similar prophylactic effects against poisoning by cyanogen chloride.

In the course of exposing a considerable number of animals we found that, with one or two rare exceptions, the animals either died promptly, that is, within periods ranging from a few minutes to hours depending on the dose, or else they recovered completely after periods of incoordination and a semi-stuperous state lasting not more than a few hours. I recall one animal which recovered from the acute effects but became blind, could not feed itself and would not swallow. This corresponds, I believe, quite well with the experience in man: Death occurs usually quite acutely or else there is complete recovery. There have been one or two reports of neurologic or psychologic derangements lasting for from one to several weeks after the acute effects of cyanide poisoning but recovery ultimately appeared to be complete.

DR. GOLD: In the brief period that remains it might be well to discuss a few of the general problems that arise in cases in which a household poison has been swallowed. Are there any questions?

DR. CATTELL: In a case in which bichloride of mercury has been taken, I wonder whether it would not be well to give a large dose of albumin or starch solution before the stomach tube is used, and follow this by an attempt to secure vomiting with the finger?

DR. GOLD: What do you think about that, Dr. Modell?

DR. MODELL: I would agree with that. I would give something by mouth if it were available and then attempt to induce vomiting.

DR. GOLD: Milk is likely to be at hand in

the household. What would you think about using that first?

DR. MODELL: Yes, milk, or eggs. Also, I have found it easy to induce vomiting by putting the finger way down into the throat.

DR. GOLD: I might add that the use of the finger is not always successful. Some patients gag a great deal when the finger is inserted but fail to expel anything from the stomach. I remember an instance in which even apomorphine failed to empty the stomach, although there was a great deal of fairly violent retching.

DR. CHARLES WHEELER: How about such household materials as mustard or soap solutions? Are they of any value? I ask that because the labels on the containers of many poisons recommend them.

VISITOR: I have tried them without much result.

DR. GOLD: Locally acting emetics are not always reliable. I remember a case in which I gave 3 teaspoonfuls of syrup of ipecac in an endeavor to terminate a paroxysm of auricular tachycardia. This is a fairly large dose. It caused intense and most distressing nausea with a cold and clammy sweat but there was a delay of nearly an hour before retching and vomiting took place. Such delay is especially likely to occur when there is food in the stomach. Of course, after an oral dose of a poison such a delay may well prove disastrous. Gargling with soapsuds is a fairly effective method of causing vomiting. It has the advantage of involving materials which can be put to use without delay. The same is true of mustard. A teaspoonful or two of mustard powder in a glass of water is fairly effective. One must bear in mind that the water should be either cold or luke-warm. The irritant oil which causes the vomiting is liberated by an enzyme in the mustard and this enzyme is inactivated by hot water. Mustard as an emetic suffers from the same defect as other local emetics, namely, the fact that the action is not sufficiently dependable and is sometimes delayed, especially when there is food in the stomach. There are few drugs or procedures which cause a patient to vomit with such certainty or speed as a dose of 4 or 5 mg. of apomorphine injected intramuscularly. You may recall that this drug was included among the contents of the doctor's bag in the therapy conference on The Doctor's Bag a few years ago.

DR. WHEELER: How long do poisons remain in the stomach? I am thinking of such materials as bichloride of mercury, iodine or roach pastes. Is it possible to make a general statement about how long they stay in the stomach which might serve as a guide to treatment?

DR. GOLD: I wonder if Dr. Cattell would try that question.

DR. CATTELL: I doubt that one could generalize because the conditions vary so greatly. Some drugs are absorbed directly from the stomach while others have to pass into the small intestine before any appreciable absorption takes place. Furthermore, the irritation produced by some drugs may make a special case to delay or to accelerate the emptying of the stomach.

DR. GOLD: I might add a word in connection with Dr. Wheeler's point on the length of time a drug remains in the stomach, and that is that food delays the emptying of the stomach and in some cases this factor may be quite significant. If one gives an animal a fatal dose of strychnine in water, it may develop convulsions and die within fifteen or twenty minutes. However, if the dose of the drug is followed by milk, the onset of toxic symptoms may be delayed three or four times as long, and because of the delay in the absorption the animal may develop some hyperexcitability but escape convulsions and survive. It is perhaps well to bear in mind that if a patient has taken a poison and if, at the moment, you do not know of a specific remedy, you may do considerable good by giving a glass of milk. Whatever the poison is there is the possibility that the absorption may be delayed. This may then be followed with more effective measures.

DR. TRAVELL: Is that because the milk closes the pylorus?

DR. GOLD: That is at least one factor in the protective action of milk.

DR. TRAVELL: I should think that would apply particularly to the alkaloids because they are not ordinarily absorbed from the stomach. They are not absorbed from an acid medium whereas many other substances are.

DR. CATTELL: Just the fact that a poison is dispersed in a large volume of liquid may account for delay in absorption. This is well illustrated by alcohol which is absorbed to a considerable extent from the stomach. The case of alcohol also illustrates the role of milk. It is well known that alcohol taken with milk produces much less marked effects.

DR. GOLD: Potassium permanganate is used a great deal for gastric lavage in the treatment of poisonings. Dr. Travell, will you tell us how one would go about using it.

DR. TRAVELL: Potassium permanganate is used for oxidation and destruction of alkaloids and other organic poisons. It is not equally effective against all of them. For example, it rapidly destroys strychnine, nicotine, physostigmine and quinine but is ineffective against caffeine, atropine, pilocarpine and cocaine. The most desirable concentration for gastric lavage is about 1:10,000. A 1:10,000 solution is clear, transparent and violet in color. The solutions which are recommended in some handbooks of toxicology are often described as pink. These may represent concentrations of about one part in a million and may not contain enough potassium permanganate to do any good. To make up a solution of a suitable concentration quickly, take about half a teaspoonful of the crystals, which weighs about 5 gm., and dissolve it in a pint of water. This produces approximately a 1 per cent solution. Two teaspoonfuls of the latter dissolved in a quart of water produce a satisfactory lavage solution, about 1:10,000.

DR. CATTELL: That is much more dilute than the concentration usually recommended.

DR. TRAVELL: The dilutions which are recommended vary from a 1:250 solution to one which is described as pink. The stronger concentrations are so irritant that they usually induce vomiting by local action.

DR. GOLD: Potassium permanganate itself is toxic. Doses of the order of 2 or 3 gm. have caused death in humans. This fact is sometimes overlooked. One well known textbook on forensic medicine recommends putting as much as 25 gm. of potassium permanganate into the stomach.

DR. CATTELL: Are we to understand that we should not use solutions stronger than 1:10,000?

DR. GOLD: If you use solutions much stronger than 1:10,000, you would induce vomiting which might not be a bad thing in a patient who swallowed a poison. But the fact is that potassium permanganate, 1:5,000, is irritating to the gastric mucous membrane and it is wise not to use one stronger than that. The 1:10,000 solution should take care of all the needs with less risk of damage.

SUMMARY

DR. GOLD: The conference today winds up our discussion of household poisonings, the first having been held a week ago. In the two periods a fairly large number of materials came under consideration: laxative pills containing strychnine, chocolate cathartics containing phenolphthalein, eyedrops containing atropine, tablets or capsules containing barbiturates, matches, cigarettes, mercury of the clinical thermometer, lead in the paint of the furniture, borax, moth balls and other moth repellents, roach poisons of phosphorus or fluoride, rat poisons of arsenic, furniture polish, shoe polish, kerosene, gasoline and a few others. This is only a small sample of all the chemicals which present problems in household poisoning, but it apparently provided us with sufficient examples of the nature of the problems to stimulate fruitful discussion. It is not uncommon that adults are poisoned accidentally by materials in the medicine

chest. There is the case of the person getting up at night to take a dose of bicarbonate of soda and finding that he has swallowed a teaspoonful of borax which not infrequently comes in similar containers, or the person groping in the dark for a few tablets of aspirin and taking in its place a few tablets of bichloride of mercury. However, the majority of the victims of household poisons are infants and children who go exploring and put into their mouths almost anything they can manage in that way. When the physician becomes involved in the case, he sometimes encounters indubitable signs of poisoning, but it seems that more often the situation is presented to him in the form of a panicky mother and a child who shows no symptoms of poisoning and wonders what the fuss is all about.

When a mother discovers her infant toying with roach paste or moth balls and dashes off to the doctor's office, she is apt to arrive without a very informative protocol as to when the patient may have swallowed the poison and how much. What the doctor is to do is not always an easy decision to make for, while in some instances the chemical involved is apparent at once, in many other cases the material may be a product of commerce, the ingredients of which are not stated on the label. Attention was called to instances in which it was virtually impossible for the doctor to secure that information. It might be suggested that he proceed directly to empty the stomach and wash it in all cases in order to play safe. Whether such practice is proper is open to question. A noteworthy point was made by one of the pediatricians at the conference who reviewed the experience at this hospital over a period of years. He found that the vast majority of these problems which are brought to the emergency room result in no poisoning even when nothing is done. One of the toxicologists at the conference made a strong point of the toxicity of fluoride, and indeed it is one of the most serious of poisonings encountered under some conditions; but the pediatrician seemed to view the subject of fluoride more lightly from his experience with numerous cases which have appeared at the clinic because the child had been toying with roach powder containing sodium fluoride. The pediatricians at the hospital here have been in the habit of observing these children for a period and then allowing them to go their way without treatment. This can only signify a kind of discrimination on the part of young children, which does not prevent them from getting the material all over their hands and perhaps tasting some but apparently not enough to do them any harm.

A knowledge of the speed of absorption of the particular chemical often supplies decisive information as to the desirability of treatment; for if an hour or two have elapsed in the case of a compound known to be absorbed in about fifteen minutes or so, the likelihood of poisoning without treatment may be considered to have become negligible. Treatment is not necessarily desirable even if symptoms of poisoning are present at the time. An example was cited of a child quite severely poisoned with atropine, for which no antidotes to the lethal action exist, and in which case attempts to overcome some of the disturbing symptoms yielded anything but favorable results. Attention was called to the fact that attempts to counteract symptoms by means of other drugs are not often fruitful, for the presenting symptoms may have little to do with the lethal action of the compound, and the drugs used in treatment may simply add to the burden of the poisoning.

In short, before one resorts to any measures in a child who has had suspicious exposure to a poison in the household, if there is little knowledge as to how much if any the child has consumed and there are no signs of poisoning, skillful temporizing, with the child under observation, is very often the most satisfactory kind of management; and a knowledge of the time which has elapsed often affords a basis for prognostication which provides both the doctor and the family with considerable relief. If symptoms or signs are present, it is

usually wise to empty and wash the stomach to prevent further absorption. But before one applies any drugs to counteract the symptoms, it should be clear as to whether such symptoms have any bearing on the lethal action of the poison; for if they have not, the patient is likely to be better off with an opportunity for the effects of the drug to wear off by elimination.

It is useful to bear in mind the point that poisons taken in the forms in which they are encountered in the household sometimes present quite a different problem from that which one might infer from the descriptions in texts on toxicology. The case of nicotine is a good example. A child may swallow the tobacco of two cigarettes which contain more than a lethal dose of nicotine, but it is likely to get into very little trouble because the first portion absorbed causes sufficient vomiting to expel the remainder of the tobacco; and there are the experiments in animals showing that nicotine in the form of tobacco taken by mouth is only about one-fifth as toxic as the poison taken as such.

There was no tendency in these conferences to minimize the hazards of disaster from household poisons, but the attention called to the relative infrequency of disasters because of the conditions under which infants and children go about the matter of sampling poisons is worth bearing in mind in order to avoid undue panic on the part of the family and overzealous treatment which may do more harm than good.

For the vast majority of poisons there are no specific antidotes. If there is reasonable suspicion that a serious quantity of poison has been consumed, delaying absorption, washing the stomach and the treatment of hazardous symptoms are obviously necessary. There was some discussion of the utility of various measures. The extraordinary efficacy of BAL as a specific antidote in the treatment of bichloride of mercury poisoning and arsenic poisoning, the various measures which prove useful in lead poisoning, and the remarkable results in the treatment of cyanide poisoning by the use of intravenous sodium thiosulfate and sodium nitrite received special attention.

Clinico-pathologic Conference

Skin Eruption, Obtundity and Pyrexia*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., and David E. Smith, Jr., M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. H., (No. 174757), an unmarried negress, sixteen years of age, who had been employed as a cotton picker, entered the Barnes Hospital on July 31, 1949. The patient was too ill to give her own history and the data available were obtained from a relative who was not well informed in regard to the patient's illness. Her chief complaint was said to be fever, drowsiness, left chest pain and a skin eruption. The family history, past history and systemic review were non-contributory. One month before coming to the hospital the patient developed a sore throat with which were associated swollen glands in the neck and a sensation of tightness in the chest. She was seen by her physician who made a diagnosis of tonsillitis. He gave the patient a green liquid medicine, and her complaints apparently disappeared in a few days; she continued, however, to take the green liquid medicine until the time of admission. After a few days, during which she was asymptomatic, the patient again developed a sore throat which apparently was so mild that she felt well enough to go on a four-day outing. During this period she was said to have had no sign of disability or feeling of ill health. Soon after her return from the outing, however, which was about two weeks before entry to the hospital, weakness and malaise appeared, and the patient was forced to take to her bed. She developed an eruption, first over the face and then over the neck and trunk, the lesions of which were described as "red, tiny, grain-like lumps." There was no associated itching but some of the nodules were tender. New lesions developed from time to time and there was regression of some of the older ones. One week before entry the patient developed pain in the left lower chest associated with a non-productive cough; she was given daily injections of penicillin by a physician. During this week her appetite failed almost completely, she complained of feverishness and she had several shaking chills. Her drowsiness increased and she was out of contact with her surroundings most of the time. There was no history of either gastrointestinal or genitourinary tract symptoms and no known exposure to either tuberculosis or syphilis. A blood test, taken at the onset of her illness, was said to have been negative.

Physical examination at the time of entry revealed a temperature of 41°C., pulse 160, respirations 65 and blood pressure 120/70. The patient was a well developed, young colored woman who appeared acutely ill and somewhat obtunded. The skin was dry. There were many raised, hard, red papules over the face, neck and trunk, but only an occasional one on the extremities. The lesions varied in size from 0.2 to 1.2 cm. in diameter and appeared to be of varying duration. Some had exfoliated and were deeply pigmented. The lesions were not vesicular; they seemed to involve both the skin and the subcutaneous tissue. (Fig. 1.) There was generalized lymphadenopathy, the nodes varying from 1 to 2 cm. in diameter. They were firm but not tender. Several

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

conjunctival lesions not unlike those on the skin were described, and in the left lower conjunctival sac there was a lesion that resembled a mucous patch. The pupils reacted normally to light and accommodation and the fundi appeared normal. The nasal mucosa was crusted and dry and several small bleeding points were seen. The lips were dry and covered with a scaling crust. The tonsils were definitely enlarged. The neck was somewhat stiff to anterior flexion. Respirations were rapid and shallow There was dullness to percussion over the left posterior lung field and lower axilla, and over this area the breath sounds were diminished and a few moist rales were heard. Examination of the heart revealed the maximum apical impulse to be in the left fifth interspace, 6 cm. from the midsternal line. There was a diffuse rippling pulsation over the entire precordium. The rhythm was regular and the first apical sound was split. No murmurs were heard. Palpation of the abdomen was unsatisfactory but there was some tenderness in the epigastrium and in the right upper quadrant. The liver was felt 6 cm. below the costal margin but the spleen was not palpable. Pelvic and rectal examinations were negative. Neurologic examination revealed hypoactive reflexes.

The laboratory findings were as follows: Blood count: red cells, 3,510,000; hemoglobin, 9.5 gm.; white cells, 25,150; differential count: juvenile forms, 4 per cent; stab forms, 22 per cent; segmented forms, 64 per cent; lymphocytes, 20 per cent. Very few platelets were seen and there were two normoblasts per 100 white cells. Urinalysis: negative. Urine culture: negative. Stool examination: guaiac negative. Blood Kahn test: negative. Blood cultures: negative. Blood chemistry: non-protein nitrogen, 19 mg. per cent; total protein, 5.8 gm. per cent; albumin, 3.5 gm. per cent; globulin, 2.3 gm. per cent; agglutinations versus typhoid, paratyphoid, brucella and tularense antigens: negative; cold agglutinin test, negative. Stool culture: no pathogenic organisms were isolated. Sputum smear: no acid-fast bacilli. Sputum culture: Staphylococcus albus, non-hemolytic streptococcus. Electrocardiogram: normal. Roentgenograms of the chest: "There is an increase in lung markings bilaterally with small fine, nodular areas of density in both lung fields interpreted as bilateral bronchopneumonia." Flat film of the abdomen: "Marked hepato-splenomegaly."

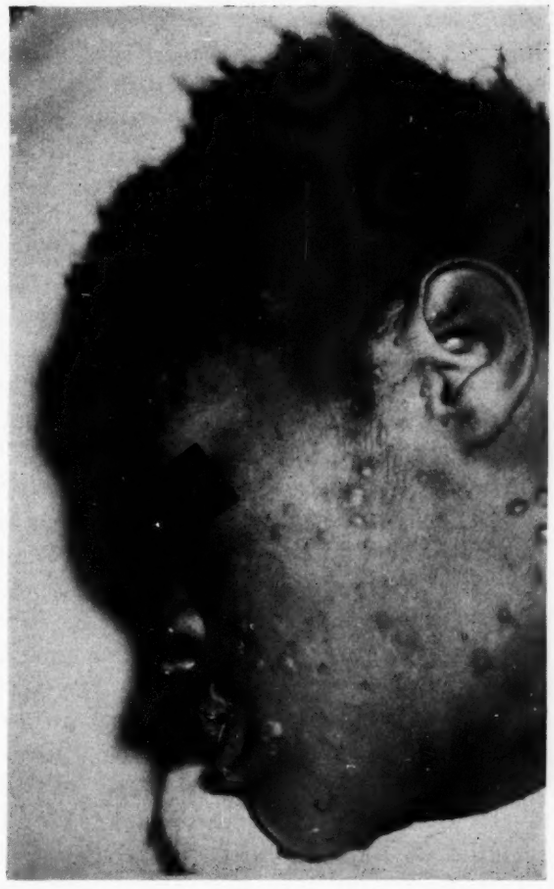


FIG. 1. Photograph of face showing the gross appearance of the skin lesions.

Soon after admission a lumbar puncture was performed. The dynamics were normal and the fluid was entirely normal. The patient was given intravenous fluids, oxygen by nasal catheter and adequate doses of penicillin, streptomycin and aureomycin. In the first twenty-four hours after admission there was little change in her condition. On the second hospital day she had a chill and her temperature spiked from 39.5° to 41°C. The signs at the left base remained unchanged. On the third hospital day her

temperature had fallen to 37.4°c. Coccioidin, histoplasmin and first strength P.P.D. skin tests were negative. Blood cultures were drawn at frequent intervals and all remained sterile.

The patient was seen in consultation by a dermatologist. He described the skin lesion as extraordinary in appearance and suggested the possibility that it might be due to bromide intoxication. The blood bromide level was then determined and found to be 200 mg. per cent; the chlorides were 101 mEq./L., and the carbon dioxide combining power 25.6 mEq./L. Liver function studies revealed the cephalin-cholesterol flocculation test to be 3+, the icterus index 4 units, and the thymol turbidity test 10 units. The Van den Bergh test was normal. The patient was also seen in consultation by the hematologic service and a sternal bone marrow aspiration was performed. There was stimulation of the myeloid cells, some shift to the left and an increase in mitotic figures. Many of the myelocytes showed vacuolization and toxic granules. Extensive search failed to reveal plasmodia, histoplasma, toxoplasma or tubercle bacilli. Another chest film was obtained and, in addition to the findings described on the original film, there was now evidence of fluid in the right pleural cavity. The infiltration at the right base had progressed and there was thickening of the minor lobar fissure on that side. The x-ray diagnosis on the basis of the second film was bilateral bronchopneumonia, right pleural effusion and pleurisy.

During the final three days of her life the patient's temperature ranged from 38.5° to 39.5°c., and her respiratory rate between 40 and 60 per minute. Fluids were forced by mouth and saline solution was given intravenously in large amounts; the blood bromide dropped to 125 mg. per cent. Antibiotic therapy was continued without evident effect. On August 6, 1949, the patient seemed quite well oriented and remarked to a nurse that she had a very good night's rest. Thirty minutes later she expired.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: When this patient was admitted she presented a very difficult diagnostic problem and we face the same problem here today. When she was first seen on the ward, it was thought by the house staff that she had an acute fulminating infection. After Dr. Weiss saw the patient in consultation and suggested brominism as the cause of the skin eruption, the situation was, if anything, even more difficult to evaluate. Dr. Hunter, had you seen this patient with the information which we have at hand now, what diagnosis would have seemed most probable to you?

DR. THOMAS H. HUNTER: Whenever one sees a young negress who is acutely ill with a disease that involves the lungs, he should consider tuberculosis. When I read the protocol, that diagnosis came to my mind and I think that disseminated tuberculosis must certainly be considered as one of the most likely probabilities. Hepatomegaly and splenomegaly are consistent with it although the leukocytosis of 25,000 with a marked left shift would be somewhat unusual. She exhibited certain evidence of central nervous system involvement; and before one knew the results of the lumbar puncture, he might also have seriously considered tuberculous meningitis.

DR. ALEXANDER: Dr. Goldman, would you comment on the occurrence of generalized lymphadenopathy in tuberculosis.

DR. ALFRED GOLDMAN: It is entirely consistent with that diagnosis.

DR. HUNTER: Could the generalized involvement of lymph nodes have resulted from the skin eruption?

DR. RICHARD S. WEISS: If the skin lesions had been the site of a secondary pyogenic infection, I would not have been surprised to find generalized lymphadenopathy. Otherwise, I would think it would be unusual.

DR. EDWARD H. REINHARD: I saw this patient just before she died. Many of the skin nodules were of considerable size.

Are discrete nodules common in bromide eruptions?

DR. WEISS: Bromide eruptions are rather peculiar and often appear in one of two forms: first, as an erythematous lesion such as erythema multiforme with urticarial phenomena and, second, as nodular granulomas such as were seen in this patient. Her lesions were discrete and many of them were keratotic on their uppermost surface. In some areas they were verrucous. Some appeared to be involuting and in a number of areas there were pigmented spots which we interpreted as sites of completely involuted lesions. When we saw the patient we were unable to associate the skin lesions with anything other than a bromide eruption. They were not at all like the nodular tuberculids which one sees in disseminated tuberculosis; for example, the centers of this girl's lesions were not necrotic and did not slough out. Furthermore, the fact that she was somewhat obtunded seemed entirely compatible with the diagnosis of bromide intoxication. It is only fair to say that although Dr. Conrad and I saw the patient independently and both made a diagnosis of bromide eruption, neither of us was completely convinced that our diagnosis was correct. When the blood bromide level of 200 mg. per cent was reported, we felt reassured. Subsequently the green medicine which she had taken was found to contain bromide. It should be mentioned, however, that patients who exhibit the systemic manifestations of bromide intoxication rarely if ever develop bromide eruptions.

DR. ALEXANDER: Does the negative first strength P.P.D. skin test rule out tuberculosis?

DR. CARL G. HARFORD: No, it does not.

DR. ALEXANDER: Dr. Grunow, do you think the findings on the chest film are suggestive of tuberculosis?

DR. OTTO H. W. GRUNOW: I should say the findings are definitely not suggestive of tuberculosis, Dr. Alexander.

STUDENT: May we ask Dr. Goldman if this patient could not possibly have had the primary type of tuberculosis?

DR. GOLDMAN: If indeed she had tuberculosis, that is probably the form in which it existed; but I doubt seriously if tuberculosis is the correct diagnosis. Histoplasmosis might have produced a clinical picture such as this patient exhibited.

DR. ALEXANDER: Your point is well taken. Certainly the combination of hepatomegaly, splenomegaly, fever and pulmonary infiltration suggests histoplasmosis. The bone marrow was studied very carefully, however, and no organisms were found. Dr. Reinhard, should they have been seen if this patient really had histoplasmosis?

DR. REINHARD: I think that it is likely that they would have been.

DR. ALEXANDER: A number of blood cultures were negative. Does the cultivation of histoplasma capsulatum require a special medium?

DR. HARFORD: No. The organism will grow in media such as is used routinely for blood cultures.

DR. ALEXANDER: Are there any other suggestions?

DR. HARFORD: Along with Dr. Goldman's suggestion of histoplasmosis, I should like to bring up for consideration the diagnosis of systemic blastomycosis. This disease is also rare but we have had one case of it in a similar conference a few years ago, and it characteristically produces pulmonary findings, subcutaneous nodules, a leukocytosis with a left shift, and one would not expect it to respond especially well to antibiotics.

DR. ALEXANDER: Certainly blastomycosis should be considered, Dr. Harford.

DR. ALBERT I. MENDELOFF: Can Dr. Reinhard assure us that this patient did not have acute Hodgkin's disease? She had a large liver and spleen and an acute fulminating course. Does the single bone marrow examination and the multiple peripheral blood examinations rule out that diagnosis?

DR. REINHARD: When I saw this patient the diagnosis of Hodgkin's disease did not suggest itself to me. However, there is

nothing in the history or course which is incompatible with it.

DR. HUNTER: Could she have had fulminating atypical pneumonia? Peculiar neurologic symptoms may occur in such patients when they are extremely ill, and one of the most prominent findings was her extraordinary tachypnea which was maintained throughout her course. Had she had atypical pneumonia she probably should have responded to the large doses of aureomycin she received; the efficacy of aureomycin in atypical pneumonia, however, is not yet proved. A leukocytosis of 25,000 is somewhat uncommon in atypical pneumonia but may occur.

DR. ALEXANDER: The negative cold agglutinins are somewhat against that diagnosis, Dr. Hunter.

DR. HUNTER: Yes, although they are positive in only 75 per cent of cases. I do not think that primary atypical pneumonia is an especially likely diagnosis but I suggest it merely because this situation is so complicated.

DR. ALEXANDER: One suggestion which was made during the patient's course in the hospital was tularemia. Dr. Wood, would you be surprised if this patient had indeed had tularemia?

DR. WOOD: It is possible that this patient had tularemic tonsillitis originally and that subsequently there was systemic spread with involvement of the lungs, the liver, the spleen and the lymph nodes. Similar cases of tularemia are well known. I have never observed a skin eruption in tularemia but in this instance the skin eruption can be explained on the basis of bromidism. The course of the disease was rather long for tularemia, however, and the patient should certainly have responded to the antibiotic therapy which she received. Finally, the negative tularense agglutination militates against the diagnosis of tularemia. Therefore, I am inclined to exclude tularemia.

DR. HENRY A. SCHROEDER: I should like to ask Dr. Weiss whether widely disseminated skin lesions of a nodular character may not occur in tularemia.

DR. WEISS: I have never seen them.

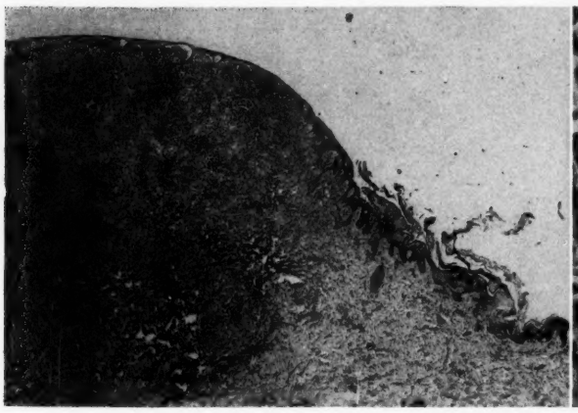
DR. EDWARD MASSIE: May I suggest as a further possibility acute bacterial endocarditis, which should be considered as one of the causes of fever of unknown origin.

DR. SEYMOUR REICHLIN: There is an interesting paradox in some of the laboratory studies. It was reported that the bromide level was 200 mg. per cent (25 mEq./L.) and the chlorides 101 mEq./L. If one calculates the total blood anions, he gets a result which totals about 175 mEq./L., which is quite unlikely. The explanation for the apparent paradox lies in the fact that the routine technic for the determination of serum chloride in our laboratory includes bromide as well. Actually the patient probably had only 75 mEq./L. of chloride and 26 of bromide.

DR. ALEXANDER: That is a very interesting bit of information. Now for purposes of discussion the fact that a skin biopsy was obtained in this case before the patient died was not included in the protocol. I shall ask Dr. Moore to tell us about the results of that biopsy.

DR. ROBERT A. MOORE: Dr. Ackerman examined the skin biopsy and made a diagnosis of reticulum cell sarcoma. Figure 2 is a section of one of the lesions. On the right relatively normal skin is shown, whereas at the left of this section a nodule is seen which extends to the epithelium. It is made up of an extremely cellular mass of tissue without necrosis. Figure 3 is a higher power view of the same section and shows the cell type found within the nodule. It is a relatively large cell with eosinophilic, moderately dense cytoplasm, a fairly large nucleus and a nucleolus. All of us who saw this slide subsequently concurred in the diagnosis of reticulum cell sarcoma.

DR. ALEXANDER: The diagnosis of reticulum cell sarcoma was certainly not suggested before the results of the biopsy were made known. I should like to congratulate Dr. Mendeloff whose suggestion of Hodgkin's disease closely approached the correct diagnosis. It is quite clear now that none of the therapeutic measures employed



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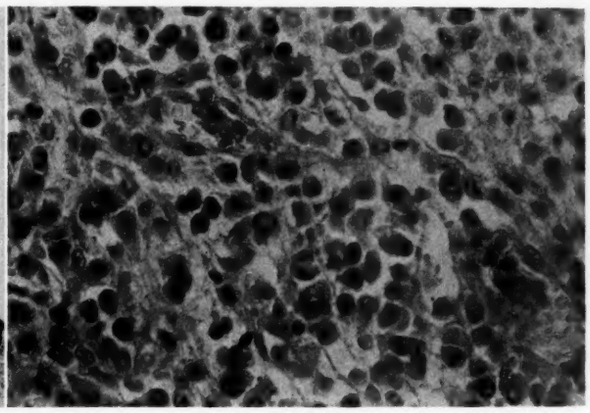

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FIG. 2. Nodule of malignant lymphoma in the skin.
FIG. 3. Detailed view of the reticulum cell type which was the infiltrating cell in all the lesions. This section is from a lymph node; but except for a variable degree of fibrosis the lesions in all sites were similar.

could have changed the course of this patient's illness and nitrogen mustard therapy was not used because she was moribund before the correct diagnosis was known.

PATHOLOGIC DISCUSSION

DR. RAYMOND F. HAIN: In addition to the papulo-nodular rash described clinically there was generalized enlargement of the lymph nodes which was most advanced in the axillary and para-aortic regions. These nodes were light gray, firm and discrete and on their cut surfaces there was an irregular cobblestone appearance that suggested coalescence of the lymphoid follicles. The liver was enlarged and weighed 2,070 gm. It was pale yellow-brown with a diffuse stippling of gray dots on the cut surface. The spleen weighed 540 gm. and was very soft. When the red pulp was scraped away, there remained tiny irregular islands of gray tissue in the pattern of the follicles. There were 300 cc. of slightly turbid yellow fluid in each pleural cavity and the pleural surfaces were covered with a soft, yellow, fibrinous exudate. Beneath the visceral pleura were numerous small foci of yellow-grey tissue. The lungs were firm, moist and heavy and together weighed 1,790 gm. The peritruncal tissues were broad and unusually prominent. In the heart there were wavy, parallel streaks of yellow fatty degeneration across the endocardial surfaces of the papillary muscles of the left ventricle. The lymphoid follicles of the colon were prominent but Peyer's patches were not. A number of superficial ulcerations of the mucosa of the stomach were present. The genitourinary tract, pancreas, adrenals and other tissues including the brain were of essentially normal gross appearance.

DR. ROBERT A. MOORE: The gross changes in the tissues of this patient were rather subtle but they suggested the presence of cells that had particularly infiltrated sites where lymphoid tissue is usually present. This infiltration had resulted in the enlarged liver and spleen with tiny gray foci in the parenchyma, the enlargement of the lymph nodes with alteration of the architectural pattern of the cut surfaces, and the presence of nodules of gray tissue beneath the pleura and similar tissue along the peritruneal tissues of the lungs. Such infiltrating tissue is most likely to be derived from the elements of the reticulo-endothelial system.

The essential type of tumor cell was identical throughout the body wherever it occurred. As previously described, it was a large cell with dense eosinophilic cytoplasm, a vesicular nucleus that frequently contained a prominent nucleolus, and various shapes that ranged from spindle to polygonal to round. In a section of the bone marrow (Fig. 4) there were foci of the same

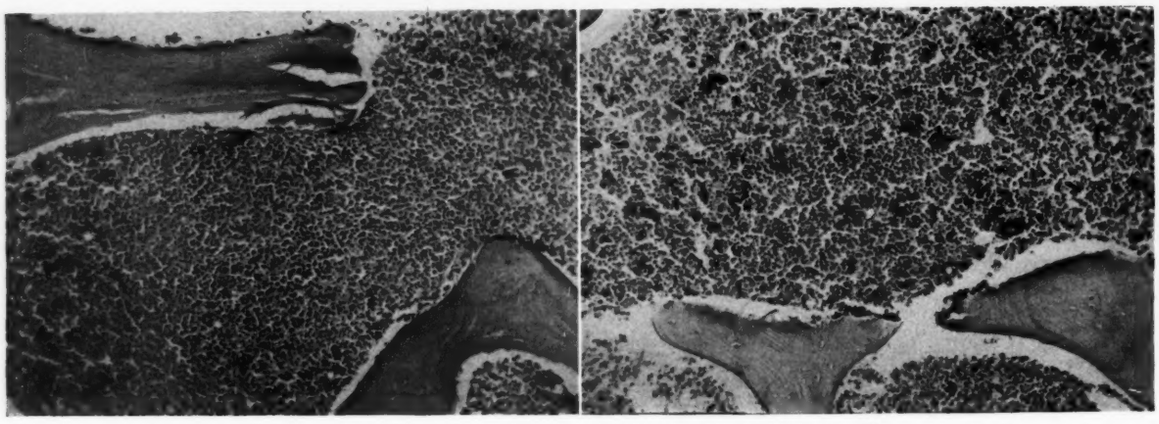

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FIG. 4. Nodule of tumor in the bone marrow.
FIG. 5. Bone marrow uninvolved by tumor but exhibiting normoblastic hyperplasia.

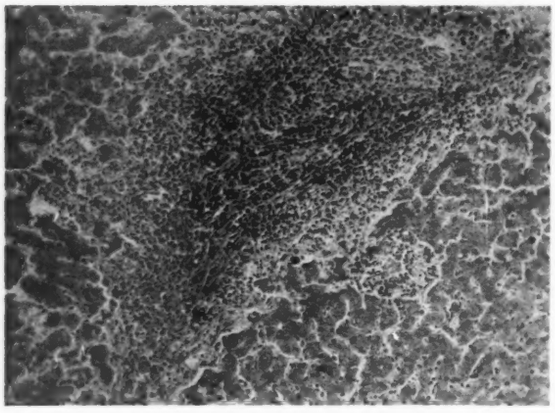

FIG. 6. Portal infiltration of the tumor cells in the liver and a small focus of acute necrosis below and to the right of the portal triad.

type of cell. In that tissue the distribution was nodular with some foci of complete replacement of the normal marrow as is illustrated while in other foci (Fig. 5) the marrow was preserved and displayed a hyperplasia of the normoblastic type that was probably associated with the anemia noted clinically.

In sections of liver (Fig. 6) there was infiltration by the same type of tumor cell into the portal spaces together with some proliferation of fibrous tissue. This latter feature and pleomorphism of the cells which occurred from place to place were suggestive of Hodgkin's disease. There were even some multinucleated cells of the Reed-Sternberg type. Just below and to the right of the infiltrated portal space in Figure 6 there is a small focus of necrosis. I do not know with what phase of this patient's disease such a small focus of acute necrosis could have been associated, but similar foci were present throughout all sections of the liver. They were not like the lesions in typhoid fever, but rather resembled those that can be observed following administration of sulfonamides or after several types of acute infection. They could possibly have resulted simply from hypoxia although usually lesions of such etiology are central rather than focal and peripheral.

In sections of the lung (Fig. 7) practically every bronchial wall was involved by the same infiltrating cell present in the other tissues. Figure 8 is an illustration of a section of the myocardium which contained a distinct and rather advanced example of the lesion which is called fragmentation of the myocardial fibers. The actual significance of this change is still doubtful after fifty or seventy-five years of debate. It was once thought to represent an actual destruction of the syncytium of the myocardial fibers and therefore to be an adequate explanation of cardiac failure, but that view was discredited. In the past decade after a period of complete scepticism, some pathologists have come to attach significance to the lesion. Most pathologists consider it as agonal and a result of the terminal event rather than its cause. Since the lesion appears after experimental intermittent

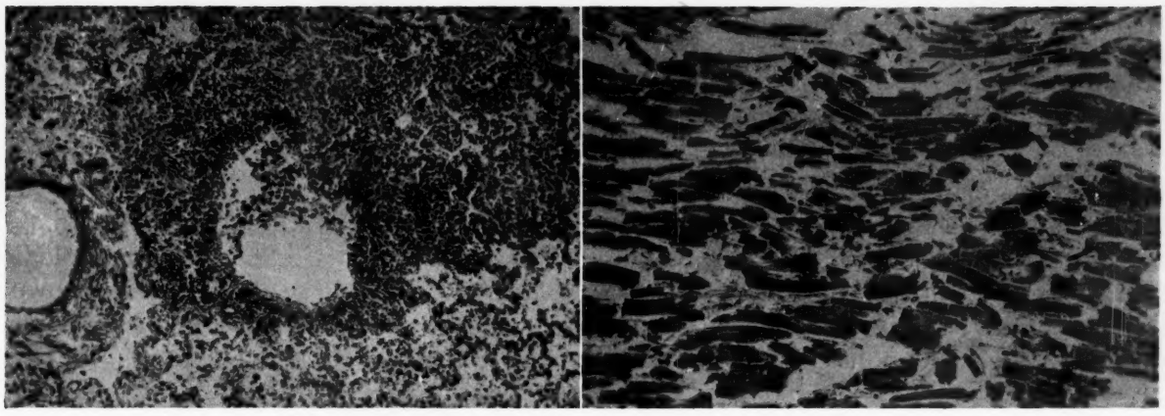

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FIG. 7. Peribronchial infiltration of tumor cells in the lung.
FIG. 8. Fragmentation of the myocardial fibers.

ligation of the ascending aorta, it seems to be related to the induction of increased pressure within the left ventricle. I regard it as indicative of sudden dilatation of the heart, at least in some cases.

The histologic changes in this case indicated this process was a neoplastic disease of cells derived from the reticulo-endothelial system. The pleomorphic features of the infiltrating cells were particularly notable on careful study of the sections and combined with the presence of fibrosis and infiltration of eosinophiles in some foci indicated that this disease was related to Hodgkin's disease. In the last century when definite concepts concerning neoplastic disease of the lymphoid system were just being developed, classification of individual cases was made rather facilely on the basis of a single observation of tissues obtained by either biopsy or autopsy. A great variety of individual histologic pictures were observed and resulted in a long list of diagnoses such as small cell lymphosarcoma, large cell lymphosarcoma, reticulum cell sarcoma, Hodgkin's disease, granulomatous Hodgkin's disease, paragranulomatous Hodgkin's disease, sarcomatous Hodgkin's disease, follicular lymphoblastoma, lymphoid leukemia and many others. More extended studies of serial biopsies from individual patients and even the study of multiple sections from the same patient have given rise to the concept that all these lesions are in fact variable morphologic expressions of a single disease which may change from time to time as the disease progresses. Dr. Custer and Dr. Burnhard had the opportunity during World War II to study material at the Army Institute of Pathology from about 1,300 patients who had some such disease of the lymphoid system. In many of the cases multiple biopsies and multiple sections from different lymph nodes were available. They came to the conclusion that the most significant manner in which a diagnosis of these conditions could be expressed was to speak of them as malignant lymphoma of one or the other of various cellular types. They found that when the numbers of cases were large enough, there was such inconstant variation in the clinical courses that no significance could be attached to the classification according to the type of cell present in any individual case. They also observed what they interpreted as transformation between various of the cell types of lymphoblastoma during the course of many cases and in their article on this subject they have constructed a chart which illustrates the various cellular types between which they observed transformation.* For instance, they observed lymphoid leukemia, lymphosarcoma and

* CUSTER, R. P. and BURNHARD, W. G. Hodgkin's disease: its relation to the other neoplasms of lymphatic tissue. *Tr. & Stud., Coll. Physicians, Philadelphia*, 15: 68, 1947.

any of the forms of Hodgkin's disease arise where there had first been only the lesions of follicular lymphoblastoma, and they observed cases in which any of the other lesions became transformed into lymphosarcoma. Monocytic leukemia was the only disease of this group in which they did not find examples of transformation except between it and reticulum cell sarcoma; but it was the one form in which they did not consider they had a statistically significant number of cases.

I have heard Dr. Custer questioned rather closely as to the prognostic significance of the diagnosis of the various cell types of this disease by a number of people who are inclined to believe that in one instance the average expectancy of life is greater than in some other instance. Dr. Custer firmly maintains that all cases are instances of the same basic disease, that the diagnosis of malignant lymphoblastoma is entirely adequate as far as any prognostic implications we are justified in making, and that the designation of the cell type predominant in a single section of tissue is simply an expression of the pathologist's opinion of the stage of the general disease in which the patient is situated at a particular moment.

Using the older criteria, we would have diagnosed the lesions in the case we have discussed today as malignant Hodgkin's disease or Hodgkin's sarcoma; but in view of the studies of Custer and Burnhard and the general tendency among pathologists to regard reticulum cell sarcoma as identical with what was formerly called Hodgkin's sarcoma, our diagnosis is malignant lymphoma of the reticulum cell type. I know Dr. Reinhard's viewpoint is at variance with some of the points I have expressed and I would appreciate his comments on the concept of these diseases as a group.

Dr. Reinhard: As long as the etiologic cause of any of these diseases is unknown, it would be hard to prove or disprove the concepts of Custer and Burnhard. To take two extreme examples, the inclusion of chronic lymphoid leukemia and monocytic leukemia within the generalizations as to prognosis is a particularly weak point in the schema. For example, a patient with all the clinical manifestations of monocytic leukemia can rarely be expected to survive as long as six months and certainly will not live any longer than five years; on the other hand, many patients with chronic lymphoid leukemia have lived considerably longer than five years.

Final Anatomic Diagnoses: Malignant lymphoma, reticulum cell type, involving lymph nodes, liver, spleen, lungs, pleura, skin, mucosa of the esophagus and stomach, lymphoic follicles of the colon and bone marrow; fatty degeneration of the myocardium; microscopic fragmentation of the myocardial fibers; hydrothorax, bilateral; congestion and edema of the lungs.

Acknowledgement: Figures 2 to 8 were made by the Department of Illustration, Washington University School of Medicine. Figure 1 was made by Mr. P. D. Reister of the fourth year class.

Special Feature

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE EASTERN SECTIONAL MEETING IN BOSTON, DECEMBER 3, 1949

CIRCULATORY EFFECTS OF THE BODY RESPIRATOR. *J. V. Maloney, Jr., M.D. (by invitation) and J. L. Whittenberger, M.D. Boston, Mass.*

The negative pressure tank respirator has been considered the most physiologic method of artificial respiration. It is generally believed to imitate normal respiration because the negative intratank pressures are associated with the normal negative pressures of the pleural space. However, close scrutiny of the mechanics of the respirator indicates that it produces respiration by pressure relationships which are mechanically and physiologically identical with those produced by applying positive pressure by mask to the patient's face, except for the negligible air density difference. During the time of no air flow at the peak of normal inspiration, the pressure within the alveolus is greater than the pressure outside the chest wall by an amount equal to the positive or negative pressure applied.

In a series of animal experiments pressure recordings taken in relation to the subject's ambient pressure demonstrate that positive airway pressure and negative intratank pressure produce identical changes in intrapulmonic, intrapleural, intracardiac and systemic arterial and venous pressures. In the presence of circulatory instability due to hemorrhage, barbiturate poisoning or medullary paralysis the body respirator causes severe circulatory depression. This depression can be eliminated largely by the use of a positive as well as negative intratank pressure phase. These results have been confirmed in a group of patients suffering from respiratory and circulatory depression of medullary origin.

The negative pressure tank respirator produces: (1) impairment of the circulation, decreased cardiac output, (2) increase in cerebral venous and cerebrospinal fluid pressure, (3) rise in venous pressure and, therefore, (4) loss of blood volume, (5) increased filling of the venous bed and arteriolar constriction.

INTERRELATION OF LYSOZYME WITH OTHER COMPONENTS OF GASTRIC SECRETION IN PEPTIC ULCER; ROLE OF LYSOZYME IN ULCERATIVE COLITIS. *Robert W. Reifenstein, M.D., Howard M. Spiro, M.D. (by invitation) and Seymour J. Gray, M.D., Ph.D. Boston, Mass.*

Studies were undertaken to clarify the relationship of lysozyme to peptic ulcer and ulcerative colitis and to evaluate the factors modifying the enzyme concentration in gastric juice, gastric tissue and fecal contents. Specimens of gastric juice were analyzed in ulcer and in normal patients before and after stimulation with histamine and other gastric stimulants. The concentration of pepsin, lysozyme, mucoproteose and mucoprotein was measured, and the pH, free and total acid, and the volume of gastric secretion were determined.

The lysozyme titer in gastric juice appears to vary directly with the mucoproteose fraction and inversely with the mucoprotein fraction. The concentration of lysozyme in the gastric juice and lysozyme content in the gastric mucosa at the ulcer site are significantly elevated in the presence of an active ulcer. The level of lysozyme appears to be diminished in the presence of a high pepsin concentration and a pH below 2.0. The fecal lysozyme concentration is increased in ulcerative colitis. Reduction of the enzyme to normal levels by inhibition with detergents does not appear to modify the clinical course of the disease.

EFFECTS OF A NEW QUATERNARY AMINE ON THE MOTILITY OF THE HUMAN COLON. *Fred Kern, Jr., M.D. and Thomas P. Almy, M.D. with the technical assistance of Natalie J. Stolk. New York, N. Y.* (From

the Department of Medicine, New York Hospital and Cornell University Medical College.)

The human colon is relatively resistant to the "antispasmodic" action of atropine and many synthetic atropine-like agents in customarily employed doses. A new quaternary ammonium salt, ethyl dimethyl beta-(9-xanthine carboxylate) ethyl ammonium chloride (Searle) has recently been found to have significant parasympatholytic activity. The effect of this drug on the function of the human sigmoid colon has been investigated in fifteen normal subjects by means of kymographic recordings from inlying balloons. When administered orally, 100 mg. of this agent almost completely abolished wave-like activity of the sigmoid for 135 to more than 300 minutes in ten of eleven experiments. During this period the usual hyperactivity of the colon secondary to the ingestion of food was blocked; 50 mg. doses affected sigmoid motility less often. The only side effects of the drug noted were dryness of the mouth and slight tachycardia.

This agent is far more effective in diminishing sigmoid contractility than is atropine in the usual clinical dosage. It appears to be as active in diminishing colonic activity as intravenous tetraethylammonium chloride; its effect is more prolonged and it is effective after oral administration.

THE BINDING OF THIOCYANATE IONS TO ALBUMIN AND ITS SIGNIFICANCE IN THE ESTIMATION OF "EXTRACELLULAR FLUID." *I. Herbert Scheinberg, M.D. and Henry J. Kowalski, M.D. Boston Mass.* (From the Department of Physical Chemistry, Massachusetts Institute of Technology, Cambridge, and the Department of Preventive Medicine, Harvard Medical School.)

The volume in which thiocyanate salts are distributed in the body has been used as a measure of "extracellular fluid." Previous experiments showed that solutions of crystalline human serum albumin bind thiocyanate ions and that the bound ions cannot diffuse through a semipermeable membrane. If such binding occurred in serum, the total thiocyanate concentration in serum, which is the quantity actually measured, would be higher than the thiocyanate concentration in the extravascular fluid. This would introduce a considerable error in the calculation of extracellular fluid volume.

Experiments are described in which normal human serum and defibrinated blood are dialyzed against thiocyanate solutions. The results show that considerable thiocyanate is bound in serum and blood. Comparison with the previous experiments shows that albumin accounts for almost all of the binding. With this information, calculation of the free, diffusible thiocyanate in serum, (SCN^-), is possible as a function of the total thiocyanate concentration, t, if the albumin concentration of the serum, m, is also known. If all concentrations are expressed as moles per kg. of water, the equation is

$$(SCN^-) = \frac{0.9t}{1 + m\left[\frac{787}{1 + 78.7(SCN^-)} + \frac{118}{1 + 3.95(SCN^-)}\right]}$$

The use of the quantity (SCN^-) in calculating "thiocyanate space" and the relation of this space to extracellular fluid volume are discussed. Similar considerations are applicable in the measurement of the distribution of any substance.

EFFECT OF ELECTRICAL STIMULATION OF THE FRONTAL CORTEX UPON THE PRODUCTION OF RENIN BY THE KIDNEYS. *H. G. Langford, M.D., J. W. Vester, M.D. and E. C. Hoff, M.D. Richmond, Va.* (From the Neurological Science Unit and Department of Medicine, Medical College of Virginia.)

E. C. Hoff et al. have shown that electrical stimulation of specific areas in the frontal lobe of the cerebral cortex of the cat will produce in 2 to 3 seconds an elevation of mean blood pressure of approximately 60 mm. Hg, lasting 30 to 60 seconds, and associated with prompt decrease in renal volume and increase in limb volume. Studies of the kidneys of these animals by the injection of India ink during stimulation have also demonstrated ischemia of the renal cortex apparently identical with that demonstrated by Trueta et al. after sciatic stimulation. If this stimulation is repeated ten to twenty times in the space of an hour, there is an elevation of the basal blood pressure of approximately 40 mm. Hg. In the present experiments the renin content of the plasma of five of these animals was studied by the method of Braun-Menendez et al.

as modified by Dexter. Two operated but unstimulated animals were studied as controls. The sera of three of these stimulated animals contained significant amounts of renin, while results obtained with the sera of two of them were equivocal. No renin could be demonstrated in the sera of the control animals.

CHANGES IN CARDIAC OUTPUT, PERIPHERAL RESISTANCE AND HEART WORK AFTER TETRAETHYLAMMONIUM AND ATROPINE. *D. Nouse, M.D. (by invitation), R. H. Lyons, M.D., C. H. Marry, M.D., S. Hoobler, M.D., R. Neligh, M.D. and Gordon Moe, M.D. Syracuse, N. Y.* (From the Dept. of Medicine, Syracuse University.)

Changes in cardiac output following the injection of tetraethylammonium and atropine were measured by the ballistocardiographic method in ten normal subjects and in ten hypertensive subjects who exhibited ballistocardiographic waves sufficiently close to normal to permit calculation of the cardiac output. Following the injection of tetraethylammonium there was a mean percentage increase in cardiac output of 20 per cent. This was associated with a pronounced decrease in peripheral resistance amounting to 25 per cent and a decrease in heart work. These changes gradually returned toward normal within the next fifteen minutes. In eight normal subjects who were given 1 mg. atropine intravenously the cardiac acceleration resulted in an increase in cardiac output with a slight fall in peripheral resistance not sufficient to decrease the work of the heart. In the comparison of these two groups it was apparent that the fall in peripheral resistance was the important factor in increasing the cardiac output after tetraethylammonium rather than cardiac acceleration.

MECHANISM OF BLOOD PRESSURE DEPRESSION FOLLOWING SODIUM DEPLETION. *Raymond S. Megibow, M.D., John J. Bookman, M.D. and Jonas H. Sirota, M.D. New York, N. Y.* (From the Metabolic and Cardiovascular-Renal Research Groups, The Mt. Sinai Hospital.)

We have demonstrated that the depressor effects of salt deprivation in hypertensives may be increased by accelerating the rate of sodium excretion through the use of mercurial diuretics. The present study constitutes an effort to elucidate the mechanism involved. Evidence is presented to show that the fall in blood pressure following mercurialization cannot be attributed to a contraction of the circulating blood volume or to a change in reactivity to angiotonin. The effects of dihydroergocornine and tetraethylammonium were evaluated microplethysmographically before and after mercurialization and it was found that the depressor and vasodilator responses to these drugs were intensified uniformly by desalting.

Based upon daily determination of the twenty-four-hour urinary sodium excretion by the flame photometer method, it was noted that the maximum decline in blood pressure developed after maximal depletion of sodium, and that any subsequent alteration in blood pressure could be correlated with variations in urinary sodium.

Adrenocortical function was assayed on the basis of the excretion of the 17-keto- and 11-oxysteroids, on the basis of the eosinophile and lymphocyte count and on the basis of blood glutathione concentration. Following mercurialization no significant changes in corticoid excretion or glutathione concentration were noted but the eosinophile and lymphocyte counts fell an average of 36 and 24 per cent, respectively. In one patient injection of ACTH during the control period was followed by a prompt transitory fall both in eosinophiles and lymphocytes. Following sodium depletion the eosinophile and lymphocyte counts fell to the levels noted after the initial injection of ACTH, and a second injection of this hormone failed to induce any further eosinophile or lymphocyte depression.

APPLICATION OF INTRACARDIAC, ESOPHAGEAL (ELECTROCARDIOGRAPHY) AND VECTORCARDIOGRAPHY TO THE PROBLEM OF THE CIRCUS MOVEMENT IN MAN. *A. Grishman, M.D., I. G. Kroop, M.D., H. L. Jaffe, M.D. and F. F. Steinberg, M.D. New York, N. Y.* (From the Mt. Sinai Hospital.)

Atrial fibrillation and flutter have been thought to result from circus movement in the atria. In dogs with atrial flutter Lewis demonstrated a circulating wave with an orbit including the orifices of the superior and inferior venae cavae. Although circus movement has not been satisfactorily demonstrated in the human heart, supporters of this theory have attempted to

prove that atrial tachycardia, flutter and fibrillation all result from circus movement. Many workers accepted the theory that atrial tachycardia is produced by one or more ectopic foci of impulse formation; others suggest that this mechanism causes atrial flutter and fibrillation. This explanation has been supported by Prinzmental et al. who demonstrated uniform spread of the contraction wave by means of high speed cinematography.

Hence, we used intracardiac leads to analyze the form of atrial complexes and determine the time interval of intrinsic deflection at various points within the atria. In patients with atrial flutter and fibrillation, one to three intracardiac electrodes were employed. Their tips were placed under fluoroscopic control, a spot film taken and then the intracardiac leads recorded simultaneously with suitable chest leads or esophageal leads at the left atrial level. The results first suggested a single focus in atrial flutter and a multifocal origin in atrial fibrillation. Vectoranalysis of one or more intracardiac leads simultaneously recorded with esophageal or chest leads using the explored points as pivots of a triangle strongly suggested a continuous circular pathway of the excitation wave in atrial flutter.

Vectorcardiograms of the instantaneous axis of the atria definitely proved the presence of a circus movement as the underlying mechanism in atrial flutter in man. The instantaneous axis of the atria obtained by means of intracardiac, esophageal and chest leads was demonstrated to follow a circular pathway continuously.

C.C.K.179 in the Prophylaxis of Cardiac Arrhythmias in the Dog.

J. R. Stanton, M.D., P. F. Ware, M.D. and J. W. Stutzman, M.D. Boston, Mass. (From the Departments of Medicine, Surgery and Pharmacology, Boston University School of Medicine.)

Recently reported studies (Bennet, Dhuner and Orth, J. Pharm. & Exper. Therap., 95: 287, 1949) on adrenalin-induced arrhythmias under cyclopropane anesthesia demonstrated that one of the dihydrogenated derivatives of the ergot alkaloids, dihydroergocornine (D.H.O.180), afforded effective protection from ventricular tachycardia when administered in doses of 0.2 to 0.4 mg./kg. In the present investigation, C.C.K.179 (Sandoz Chemical Company), a recently introduced combination of equal amounts of three of the dihydrogenated derivatives of ergot (dihydroergokryptine, dihydroergocristine, and dihydroergocornine), has been studied under standard conditions. Twenty-seven experiments have been carried out on thirteen dogs with complete control data in ten of the thirteen dogs. On the basis of this work, C.C.K.179 in a dose of 0.1 mg./kg. appears to be an effective protective agent. Protection appears not before twenty-five but within forty minutes after intravenous administration of the compound, and is shown to be present for at least two and one-half hours thereafter. Significant to complete protection of the heart from ventricular tachycardia was obtained during test periods in all thirteen animals following the administration of C.C.K.179. Four of ten dogs died of ventricular fibrillation during their control studies.

Pulmonary "Capillary" Pressure as an Index of Left Atrial Mean Pressure in Dogs.

R. Gorlin, M.D. (by invitation), J. W. Dow, M.D., H. K. Hellems, M.D. and L. Dexter, M.D. Boston, Mass. (From the Peter Bent Brigham Hospital.)

In dogs anesthetized with nembutal, No. 7 Cournand catheters were inserted under fluoroscopic control (1) via the jugular vein into the pulmonary artery and advanced to occlude a terminal branch and (2) via the femoral artery through the left ventricle into the left atrium. Pressures were recorded in these areas by Sanborn electromanometers. Observations were made with normal and altered pulmonary blood volumes. Mean pressures in pulmonary "capillaries" and left atrium were equal within the error of the method under all conditions studied.

Pressure in the left atrium cannot be measured directly by right heart catheterization. A pressure related to pulmonary capillary pressure has been recorded previously distal to the occluding catheter tip in the manner described. Values thus obtained are thought to be a few millimeters of mercury less than true capillary pressures. The apparent agreement between mean pressures measured in pulmonary "capillaries" and left atrium may be explained by the fact that the gradient from pulmonary "capillary" to left atrium approximately equals the error of measurement of pressure in the pulmonary capillaries. It is apparent that, in dogs,

pressure as measured in the pulmonary "capillaries" affords a reliable index of mean pressure in the left atrium.

THE SIGNIFICANCE OF FATTY INFILTRATION OF THE LIVER IN DIABETES MELLITUS. *H. J. Zimmerman, M.D., F. G. MacMurray, M.D. (by invitation), H. Rappaport, M.D. and L. K. Alpert, M.D. Washington, D.C.*

Twenty-five patients with diabetes mellitus were studied to determine the possible interrelationships of fatty infiltration of the liver, sensitivity to insulin, level of blood cholesterol, age of the patient and presence of obesity. Needle biposies of the liver were performed in each case, as well as glucose-insulin tolerance tests, blood cholesterol determinations and calculations of deviation from normal weight.

In thirteen patients fatty infiltration of the liver was found, varying from slight to extensive. A positive correlation was found between the presence of fat in the liver on the one hand and insulin insensitivity and advancing age on the other. The presence of obesity also seemed positively correlated with the presence of fatty liver, although to a less significant degree. The duration of the diabetes showed even less correlation while there seemed to be no correlation at all between the presence or absence of fat and the height of the blood cholesterol.

EXPERIMENTAL AND CLINICAL STUDIES ON THE "TRUETA SHUNT" PHENOMENA IN THE KIDNEY. *J. H. Moyer, M.D., Clark Kelly, M.D., Herbert Wendell, M.D. and Hadley Conn, M.D. Philadelphia, Pa.* (From the University of Pennsylvania.)

Three patients with non-obstructive, unilateral anuria for two to four days following the passage of small calculi were studied for evidence of the "Trueta shunt phenomena." Cystoscopy revealed no residual obstruction on the involved side. Urine flowed freely from the contralateral ureters. Spontaneous excretion of urine occurred from the involved kidney after two to four days without further manipulation or the passage of any additional calculi. On admission intravenous diodrast showed complete lack of concentration on the involved side and normal concentration on the contralateral side. After relief of the apparent "reflex shut down," repeated diodrast studies showed normal concentrations in the involved kidney in all three patients. Comparison of the oxygen content of arterial and renal venous blood during the anuria, within one week after return of function, showed no arterialization of blood in the renal vein (as reported in rabbits by Trueta et al.). The A-R O_2 difference was increased somewhat but not significantly so, due to a decrease in the renal venous blood oxygen content. This was interpreted as evidence against the operation of a "renal shunt."

Studies on renal arteriovenous blood oxygen content and renal blood flow following sciatic nerve stimulation were undertaken on sixteen dogs and twenty-one rabbits. Following stimulation the blood flow decreased and the A-R O_2 increased due to a decreased content of the oxygen in the renal venous blood in all instances both by comparison with the control period for the stimulated animals and with a control group of animals similarly prepared but not stimulated. Thus the laboratory studies substantiated the previous clinical findings.

ELECTROPHORETIC PATTERNS OF CARBONMONOXYHEMOGLOBIN IN NORMAL AND IN SICKLEMIA SUBJECTS, *R. V. Bowers, M.A., M.Sc. (by invitation), and G. Watson James, III, M.D. Richmond, Va.* (From the Medical College of Va.)

The electrophoretic conduct of hemoglobin proteins from healthy white and Negro subjects, and from Negro sicklemia patients with the trait, with the active disease and in crisis, was reinvestigated employing the Tiselius electrophoretic apparatus. Carbonmonoxyhemoglobin was prepared from washed red blood cell hemolysates and electrophoresed in phosphate buffer at 0.08 ionic strength at pH of 7.2. The electrophoretic patterns of carbonmonoxyhemoglobin from eight normal subjects (two of each blood type) exhibited two distinct fractions which migrated toward the anode. Fraction I, a slower moving component, comprised from 3.6 to 14.1 per cent of the total electrophoretic pattern, and Fraction II, the faster component, occupied the remaining 85.9 to 96.4 per cent of the total area. The outstanding difference between the patterns of our normal subjects and sicklemia patients was the markedly increased concentration of Fraction I, now occupying from 26.9 to 71.9 per cent of the total electrophoretic area. Mobility values were not significantly

different. One patient in crisis, studied before and after transfusion, showed a distinct increase in Fraction II following two pints of blood in five days.

These data indicate the presence of two protein fractions in normal red blood cell hemolysates and a distinct change in sicklemia subjects. This finding is attributed to a possible difference in the globin fraction of the hemoglobin molecule.

USE OF VITAMIN B_{12b} IN PERNICIOUS ANEMIA. *Janet Watson, M.D., Herbert Lichtman, M.D. (by invitation), Victor Ginsberg, M.D. (by invitation), and J. V. Pierce, M.S. (by invitation), E. L. R. Stokstad, Ph.D. (by invitation) and T. H. Jukes, Ph.D. (by invitation). Brooklyn, N. Y.* (From the Department of Medicine, Kings County Hospital, and Lederle Laboratories, Pearl River, N.Y.)

By fractionation of cultures of Streptomyces aureofaciens a red crystalline compound "vitamin B_{12b}" was isolated and was shown to differ from vitamin B_{12} as demonstrated by its chromatographic behavior and its ultra-violet and visible absorption spectra. Vitamin B_{12b} was found to be approximately as active as vitamin B_{12} in assays with chicks and with L. leichmanii 313. A solution of crystalline B_{12b}, 10 micrograms per ml., was prepared in 0.9 per cent sodium chloride and sterilized by filtration. This material was used for assay in four patients with Addisonian pernicious anemia. Of two who were given 1 gamma daily intramuscularly, one responded both with a reticulocyte peak and a red cell rise higher than the expected standard, and the other gave a submaximal reticulocyte response with a maximal red cell rise at three weeks. Two other patients were given 1½ and 2 gamma daily by injection, respectively. Hematologic response was again satisfactory. Clinical improvement including neurologic was excellent in all patients. It is concluded that 1 to 2 gamma of vitamin B_{12b} daily intramuscularly is hemopoietically equivalent to one U.S.P. unit of liver extract and is comparable in potency to vitamin B_{12}. Another patient who had pernicious anemia of pregnancy failed to respond to large amounts of refined liver extract and then also failed to respond to 1 gamma of vitamin B_{12b} daily but gave a very dramatic response to the subsequent daily injection of 15 mg. of folic acid. Studies on the oral administration of vitamin B_{12b} in Addisonian pernicious anemia are under way.

MICROSPECTROPHOTOMETRIC DETERMINATION OF DESOXYRIBOSE NUCLEIC ACIDS IN PERNICIOUS ANEMIA. *Edward H. Reisner, Jr., M.D. and (by invitation) Roy Korson, M.D.* (From the New York University, Post-Graduate School of Medicine and the Dept. of Zoology, Columbia University.)

The fact that the growth requirements of certain bacteria for vitamin B_{12} can be replaced by various desoxyribosides led to the hypothesis that one of the functions of B_{12} was to act as a coenzyme in the synthesis of these constituents of nucleic acids. The concentration of desoxyribosenucleic acids (DNA) in the nuclei of megaloblasts of pernicious anemia before and after treatment was therefore investigated using the microspectrophotometric technic of Caspersson as modified by Pollister. Marrow smears of approximately uniform thickness were fixed and stained with the Feulgen stain and, in some instances, with methyl green. These stains are specific for total DNA and polymerized DNA, respectively. Ten cell nuclei of 9.5 micron diameter were measured in each smear in nine cases: pernicious anemia five, juvenile pernicious anemia, two, nutritional macrocytic anemia and megaloblastic anemia of infancy, before and after treatment, and compared with each other and a normal. There was no significant difference in the concentration of DNA in any of the slides before or after treatment. The quantity of DNA is a measurement of the chromosomal makeup of the cell nucleus, which would not be expected to change in a patient with pernicious anemia following treatment. It has been shown by others that in polyploidy the DNA is proportional to the increase in the number of chromosomes, e.g., diploid, tetraploid, octaploid. This work does not exclude the possibility that lack of the enzymes essential for rapid DNA formation would prevent the formation of the extra amounts of DNA required for mitosis and bring about the condition of retarded blood formation observed in pernicious anemia.

AN EXAMPLE OF CELLULAR HYPEROSMOLARITY. *Louis G. Welt, M.D., Jack Orloff, M.D., David M. Kydd, M.D. and Jane E. Oltman, M.D., New Haven and Newtown,*

Conn. (Introduced by Jack D. Rosenbaum, M.D., Framingham, Mass.)

Acute observations were made in seven patients during twelve episodes of electroshock. Venous blood was obtained just before, at the cessation of and two minutes after the electroshock convulsion which lasted approximately sixty seconds. Serum was analyzed for sodium, chloride, potassium and total proteins. At the cessation of seven convulsions, unmodified by curare, there was an increase in the concentration of sodium in the extracellular water varying from 7.1 to 17.1 mEq./L. The calculated decrease in chloride space varied from 3.5 to 9.3 per cent. There were no significant exchanges of sodium between cellular and extracellular water. Two minutes after cessation of the convulsion the chloride space had re-expanded. During the convulsion there appeared to be a small transfer of potassium from the cells, and in the next two minutes approximately twice that amount moved into cells. These alterations are distinctly modified with reduction in the intensity of the convulsion by curare.

Associated with the muscular exercise there must be a large and rapid increase in the concentration of osmotically active constituents within the cells. In the re-adjustment of osmotic equilibrium water must move from the extracellular space into the cells.

FLUID AND ELECTROLYTE BALANCE IN THE MANAGEMENT OF ACUTE RENAL INSUFFICIENCY. *L. T. Iseri, M.D., A. J. Boyle, Ph.D., M.D. (by invitation), T. M. Batchelor, M.D. (by invitation), S. D. Jacobson, M.D. and Gordon Myers, M.D. Detroit, Mich.*

Studies of Na, K, Cl, N and water balance were carried out for periods of four to sixteen days in four cases of lower nephron nephrosis; studies of sodium and water balance were continued for longer periods in these patients and in six additional cases. Extracellular-intracellular partition of water and electrolytes was carried out according to the method of Darrow.

Marked fall in plasma sodium was encountered (1) during the oliguric phase, due partly to dilution of extracellular fluid and partly to intracellular migration and (2) during the diuretic phase due to the inability of the damaged tubules to retain sodium. Spontaneous resumption of capacity to conserve sodium tended to occur about five to seven days after onset of diuresis. Utilization of plasma sodium levels and fluid balance as a guide to treatment will be illustrated.

The plasma potassium did not rise to toxic levels in these cases. In one patient who went through ten days of extreme oliguria following circulatory collapse due to diabetic coma the plasma potassium remained below toxic levels as a result of intracellular uptake of potassium which was released from endogenous protein catabolism. Impairment in capacity to conserve potassium was demonstrated during the diuretic phase and in some cases necessitated administration of supplementary potassium chloride to combat hypopotassemia.

CONTINUOUS INTRAVENOUS INFUSION OF HISTAMINE AND METHACHOLINE IN ASTHMATIC SUBJECTS. *Job E. Fuchs, M.D. Boston, Mass. and J. J. Curry, Washington, D.C.* (From Boston University and Georgetown University.)

In an attempt to produce experimentally a steady asthmatic state as measured by a constant reduction in vital capacity, histamine and methacholine were administered to symptom-free asthmatic subjects by continuous intravenous infusion. Thirteen tests were made in nine patients using a solution of 1 microgram/cc. of histamine base at a rate of 2 to 10 micrograms/min. The reaction to the onset of a continuous infusion was a temporary asthma-like attack accompanied by a reduction in vital capacity, but followed by a return to normal within ten minutes although the infusion was continued at the same rate. The rate of infusion was limited only by the appearance of histamine headaches. Systemic effects roughly paralleled the respiratory symptoms.

Twelve tests were made in nine patients using a solution of 40 micrograms/cc. methacholine chloride at a rate of 18 to 475 micrograms/min. Except in three instances reductions in vital capacities were roughly proportional to the infusion rate. In three of five cases in which step-wise increases in infusion rate were given, progressive reductions in vital capacity were obtained and in these (and in a fourth case maintained on a constant infusion) steady asthma-like attacks with reasonably constant

vital capacities were maintained for twenty to thirty minutes.

From these studies it appears unlikely that histamine is responsible for maintained asthmatic attacks, unless it occurs in the lungs in rapidly increasing amounts or in greater concentration than obtained in these tests. In selected cases a steady asthma-like state can be produced by a constant intravenous infusion of methacholine.

QUANTITATIVE STUDIES ON PULMONARY ABSORPTION OF p-AMINO HIPPURATE AEROSOLS. *Wm. Franklin, M.D., Clarence Denton, M.D. and F. C. Lowell, M.D. Boston, Mass* (From Boston University.)

A method of determining quantitatively the amount of inhaled aerosol retained in the respiratory tract is needed in the study of drugs administered by this route and in the study of the effect of aerosolized allergenic extracts in bronchial asthma. Aerosols of NaPAH, a substance which is easily determined chemically, well tolerated, rapidly absorbed and quantitatively excreted in the urine, were studied. The procedure consisted in (1) exposing a subject to a measured volume and concentration of an aerosol of NaPAH, (2) collecting the material not retained by the subject, and (3) collecting the urine over a six-hour period to determine the total amount of PAH retained. The aerosol, produced in a nebulizer receiving oxygen at an accurately measured rate and dried by passing over concentrated sulfuric acid in order to increase its stability, passed through a flutter valve to the subject. A spirometer connected between drying bottles and flutter valve provided for the intermittent removal of aerosol by respiration. Expired aerosol passed through a second flutter valve and was collected in an impinger. Measurements were made of the PAH delivered, the PAH in the urine, the valve assembly and in the collecting impinger.

In five tests in which approximately 100 mg. were inhaled by the patient, the sum of the amounts found in the urine, the expired air and valve assembly ranged from 93 to 101 per cent of the PAH delivered, 39 to 50 per cent being recovered in the urine.

ACUTE HEMORRHAGIC ANTITHROMBOPLASTINEMIA. *Frederick Stohlman, M.D., Charles B. Crow, M.D., Jane F. Desforges, M.D.* and *William J. Harrington, M.D. Boston, Mass.* (First and Third Medical Services, Boston City Hospital.)

A defect in the hemostatic mechanism was found during studies on an elderly female manifesting an acute severe generalized hemorrhagic diathesis. This defect consisted of the presence of a potent thermolabile apparently homologous species-specific thromboplastin inhibitor in her plasma. Normal values were obtained for the following: Ac globulin, antithrombin, fibrinogen reactivity, fibrinogen, capillary fragility, platelet count, clot retraction, fibrinolysis and glass-clotting time. The silicone-clotting time, however, was prolonged to three times normal. The prothrombin activity using rabbit brain thromboplastin was normal. Use of human brain thromboplastin, however, gave a value of 14 per cent of normal and was repeatedly in this range. A mixture of aliquots of the patient's and normal plasma also gave prothrombin times which were normal with rabbit brain thromboplastin and prolonged with human brain thromboplastin. The inhibitor effect was immediate; it was not increased on incubating the patient's plasma with thromboplastin. The patient's prothrombin-free plasma to which standard bovine prothrombin was added inhibited human thromboplastin, excluding the patient's prothrombin as a factor. The patient's plasma gave normal prothrombin times using thromboplastins obtained from the brains of dog, rabbit, sheep and steer and Russell viper venom. Thromboplastins from several brains, including that of the patient, were all inhibited.

The inhibitor was dissipated slowly on refrigeration but rapidly at 37°C., a finding borne out also on prothrombin consumption determinations. It retained activity over a wide range of pH alterations. It could be diluted out, being ineffective in 12½ plasma. It was not active against the ether extractable (cephalin) fraction of thromboplastin. It was equally effective against strong and dilute human thromboplastin. It is believed this represents a previously unrecognized hemorrhagic diathesis.

Case Report

Chiari's Syndrome: Hepatic Vein Occlusion

A Case of Multiple Venous Thromboses

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New York, New York

FIFTY years ago Chiari[1] described the symptomatology of hepatic vein occlusion. This consists typically of abdominal pain, enlargement of the liver and ascites. The course is usually rapidly fatal but occasionally long drawn out. In Chiari's three cases the pathologic lesion was an obliteration of the hepatic veins which he interpreted as due to an endophlebitis leading progressively to stenosis and occlusion. Since that time the term Chiari's syndrome has come to be applied to hepatic vein occlusion not only by primary endophlebitis but from obstruction of any cause.

Thompson[2] recently has reviewed the clinical and pathologic findings in over 100 cases in the literature. The clinical findings have been fairly constant but the pathology has been varied. The obstruction may be only in the hepatic veins or may involve the inferior vena cava as well. It may be caused by local disease such as abscess or tumor or it may be a manifestation of a general disease process such as thrombosis in polycythemia vera.[3] In many cases, as in those described by Chiari, the obstruction seems to be due to primary disease of the hepatic veins. Even here it may be a local manifestation of a systemic disease for Coronini and Oberson,[4] from careful histologic examination of eleven such cases, found a primary inflammation of veins and capillaries in other organs in addition to the liver.

In the case to be presented here the primary disease was characterized by multiple recurrent thromboses. The predominant pathologic lesion was an hepatic vein thrombosis with obstruction of the inferior vena cava as well. The clinical picture of hepatic vein occlusion was complicated by concurrent endocarditis. The patient's collateral circulation was sufficient to compensate for these lesions until a secondary portal vein thrombosis developed. Terminally there was thrombosis of the renal veins.

CASE REPORT

The patient, T. C., (Goldwater Memorial Hospital, No. 12928), was a young man of Irish extraction, twenty-six years old at the time of his death. He had been a weekend-spree drinker since the age of sixteen but his diet had in general been adequate. He had never had jaundice or other evidence of liver disease. There was no history suggesting nephritis or rheumatism. There had been no exposure to toxic agents other than alcohol. At the age of sixteen he began to have dyspnea and palpitation on exertion. One year later he complained of attacks of pain in the calves of his legs on exertion and occasional swelling of the ankles. On one occasion minor trauma led to marked pain and swelling of the right leg which lasted for two weeks and required several days' rest in bed. At the age of nineteen leg ulcers developed first on the right but later on both legs. These symptoms of ulceration, pain and swelling of the legs, dyspnea and palpitation continued but he was twenty-one before he sought medical advice. During the next three years he received a variety of local treatments for the ulcers with no lasting improvement.

At the end of July, 1946, when he was twenty-

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four years old, he noted malaise and anorexia and began to have evening fever accompanied by shaking chills. The exertional dyspnea and palpitations increased. On about August 1st he began to have gnawing pain in his stomach and back, sometimes severe enough to double him up. There was no accompanying nausea, vomiting or bowel disturbance. He went to his doctor who found an enlarged liver and referred him to another hospital where he was admitted on August 7, 1946. At that time he appeared chronically ill. His temperature was 103°F. on admission. The heart was enlarged. There was an apical systolic murmur, a questionable apical diastolic murmur and also a basal systolic murmur. The abdomen was distended but there were no signs of ascites. The liver and spleen could not be felt but there was tenderness in the right upper quadrant and in the epigastrium. The superficial abdominal vessels were dilated. There were ulcers and edema of both ankles. The red blood cell count was 2.96 million and the hemoglobin was 7.5 gm. per cent. The white count was 9,500 with 78 per cent polymorphonuclears. The urine was normal except for a few white cells. It was thought the patient had rheumatic heart disease and subacute bacterial endocarditis and possibly cirrhosis.

The patient was treated with penicillin at once. The abdominal pain gradually subsided. A week after admission the basal systolic and apical diastolic murmurs were no longer heard. The abdominal signs were unchanged. After three weeks of penicillin therapy and four blood transfusions the patient's temperature, which had risen to about 103° nightly, fell to the range of 99° to 100°. The leg ulcers healed during this time and the patient felt much better. The red count had risen to 3.8 million with hemoglobin of 10.8 gm. The abdominal distention had subsided. The liver was now palpable four fingerbreadths below the costal margin. The spleen was not felt. After a week of relatively normal temperatures without penicillin therapy the patient was allowed out of bed. However, the swelling of the ankles and abdomen recurred and there were now definite signs of ascites. The cephalin flocculation test was negative. A diagnostic paracentesis was done with the removal of 350 cc. of fluid which was not remarkable in any way.

At the end of September the patient's fever recurred and penicillin therapy was resumed. During this course a painful bluish spot appeared in the left thenar area, suggestive of an embolus. One definite petechia was noted on the neck. After two weeks of treatment the temperature again fell to normal but penicillin was maintained for a full month after defervescence. The patient now felt almost well although there was still evidence of ascites. The red count rose further to 4.86 million with 11.3 gm. of hemoglobin. There was no recurrence of fever during two further weeks of observation before discharge at the end of November. Numerous blood cultures were taken during his stay; all were sterile. In an attempt to investigate possible causes for the fever other than subacute bacterial endocarditis the following were done, namely, agglutinations for typhoid, paratyphoid A and B, Brucella abortus and Proteus OX19; all were negative. A red cell sickling test was negative. A muscle biopsy was reported to show chronic myositis and intimal thickening of the walls of the medium-sized arterioles but showed no evidence of periarteritis.

The patient was discharged from the hospital considerably improved on November 26, 1946. The diagnosis was Laennec's cirrhosis. There was thought to be insufficient evidence for the diagnosis of endocarditis. The fever was explained on the basis of thrombophlebitis.

The patient's abdomen became swollen again at home and on December 9, 1946, he entered the Presbyterian Hospital, New York. Physical examination showed a normal-sized heart with apical and basal systolic murmurs, a distended abdomen with signs of fluid, an enlarged liver and marked peripheral edema. There were distended veins along the sides of the abdomen running from the inguinal ligaments to the axillas. The blood flow in these vessels was thought to be upward. The red count was 4.34 million with 10 gm. of hemoglobin. The white count was normal. The cephalin flocculation test was 3+. The BSP test showed 15 per cent retention. The serum albumin was 3.8 and the serum globulin 2.7 gm. per cent. The serum alkaline phosphatase was twelve Bodansky units. The urine showed 1+ albumin but was otherwise normal. The blood urea nitrogen was 10 mg. per cent. A phenolsulfonphthalein test showed 70 per cent excretion in two hours. These values were unchanged on repeated determinations.

The clinical picture was thought to suggest inferior vena caval thrombosis rather than Laennec's cirrhosis. In an attempt to confirm

this simultaneous blood sugars were taken from the arm and from an abdominal collateral vein, half an hour after taking 100 gm. of glucose by mouth. If the collaterals were connected with the portal system, their blood should have a higher sugar level than the blood from the arm.[5] Actually the difference was the reverse of this, abdominal vein 111 mg. per cent and arm vein 125 mg. per cent. Venography was attempted on two occasions. Contrast medium was injected by catheter into the saphenous vein near the groin first on one side and then the other. In each case the catheter could not be introduced beyond the saphenofemoral junction. Dye was not seen by x-ray in the femoral-iliac-caval system but passed readily into the abdominal collaterals. The results were interpreted as showing a block in the femoral veins.

During his stay at the Presbyterian Hospital the patient's course was marked by fairly rapid accumulation of ascites. Four paracenteses were done. The patient was comfortable except when ascites was marked and he had a good appetite. In late December, 1946, and early January, 1947, he had a temperature of 101°F. to 102° for which no cause could be found. This returned to normal on symptomatic treatment. The patient was transferred to Goldwater Memorial Hospital on February 10, 1947, for long term care.

The sudden onset of abdominal swelling with pain and the type of abdominal collateral circulation suggested the diagnosis of inferior vena caval thrombosis. The differential blood sugars and the venograms were thought to support this diagnosis. It was believed that the 3+ cephalin-flocculation test pointed to liver disease over and above that which might be produced by congestion of the liver from inferior vena caval block or even from hepatic vein thrombosis.

On admission to Goldwater Memorial Hospital the patient looked thin and pale but had no complaints. The heart was not enlarged and only an apical systolic murmur could be heard. The abdomen was moderately distended with fluid and presented the previously described dilated veins. The liver was enlarged four finger-breadths below the costal margin and was slightly tender. For the first time the spleen was palpable two fingerbreadths below the rib margin. The legs showed brown pigmentation and brawny edema. The red cell count was 4.4 million with 13 gm. of hemoglobin. The white count showed a mild leucopenia. The urine contained 2+ albumin with occasional white cells and casts. The blood urea nitrogen was 17 mg. per cent. A phenolsulfonphthalein test showed 85 per cent excretion in two hours. The antistreptolysin titer was 250. The serum albumin was 4.4 gm. per cent, serum globulin 2.5 gm. per cent. The total cholesterol was 138 mg. per cent with cholesterol esters of 88 mg. per cent. A BSP test showed 15 per cent retention in thirty minutes. The cephalin-flocculation test was 4+. The prothrombin time was twenty-seven seconds. The bleeding time was four minutes and the clotting time twenty-five minutes. The platelet count was 150,000 per cu. mm. A capillary fragility test was markedly positive.

The diagnosis of thrombosis of the inferior vena cava was accepted. Whether the ascites and changes in the serum indicative of liver damage were due to hepatic vein occlusion or to cirrhosis was not decided. The cause of thrombosis in the face of prolonged prothrombin and clotting times and low platelet count was not clear. The patient was given intramuscular mercurial diuretics with a very good response. Over a period of four and a half months the accumulation of ascitic fluid was completely controlled without paracentesis. At that time peripheral edema had disappeared and accumulation of ascites had stopped. Some abdominal fluid remained but this disappeared in another three months. This improvement took place without significant change in any of the laboratory findings except for a return of the capillary fragility test to normal. By the end of 1947 the patient looked and felt almost well. The enlarged liver and spleen and the abdominal collateral veins persisted. There was no ascites or edema. The albuminuria had disappeared. Disturbing factors were a drop in the red count to 3.3 million with 10.4 gm. of hemoglobin and a fall of the serum albumin to 3.4 gm. per cent.

In January and February, 1948, there was a slow gain in weight as edema and ascites reappeared. At the end of February thrombophlebitis of the left leg suddenly developed in the patient, with pain, redness, swelling and high fever. This was treated with penicillin, sulfadiazine and heparin. It responded only partially to treatment and continued to smolder for the next three months. Several acute flare-ups were treated again with sulfadiazine and heparin without noticeable effect on the basic process. During these attacks the prothrombin time was

prolonged, as before, but the clotting time had returned to normal.

Mercurial diuretics were administered again in March, 1947, and were effective in controlling fluid retention for about six weeks. In May, however, two paracenteses were necessary. The patient appeared to be losing flesh rapidly at this time and after the third paracentesis at the end of June his weight was 25 pounds below that of six months before when no ascites or edema was present. His serum albumin had fallen to 2.5 gm. per cent without any other significant change in the blood. The liver was now a little larger and quite tender.

A fourth tap was done in the middle of July. Mercurial diuretics were discontinued at this time because they were ineffectual. Two days after this tap the patient went into a stupor, with nausea, vomiting and oliguria. The urine showed 2+ albumin with many red cells, white cells and casts. The blood urea nitrogen was 59 mg. per cent. It was thought that this episode probably represented an extension of the caval thrombosis to involve the renal veins but on the possibility that it might be due to mercury poisoning from the diuretic administered a course of BAL was given. The patient was maintained on intravenous fluids and during the next week the stupor lightened partially, vomiting stopped and urine output increased. He complained frequently of pain in the lumbar region. The blood urea nitrogen rose reaching a value of 144 mg. per cent. The patient continued in this state for four weeks more but eventually lapsed into coma, pulmonary edema developed and the patient died on August 27, 1948.

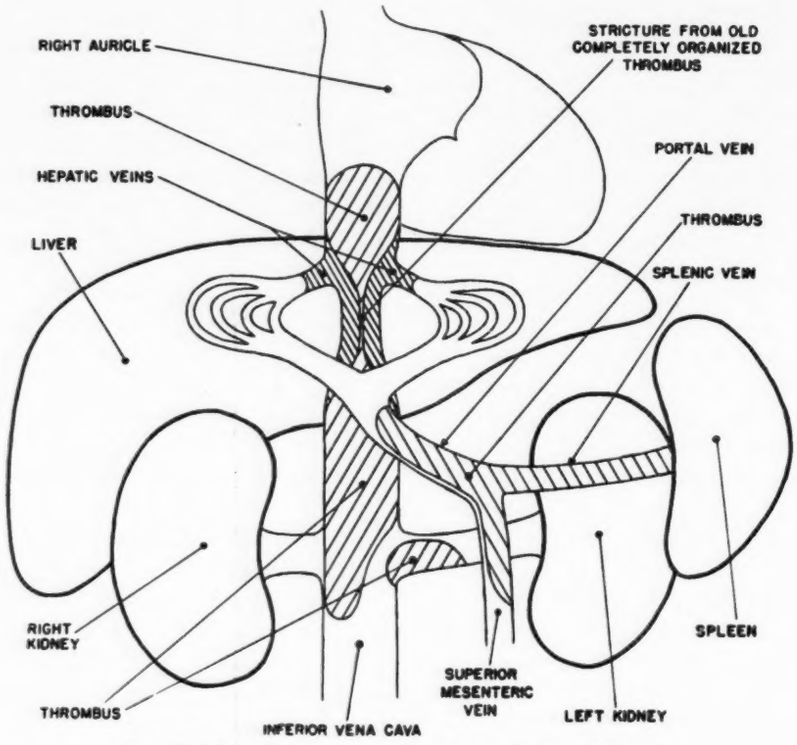

FIG. 1. Diagram of venous thromboses in the abdomen.

The clinical diagnosis was thrombosis of the inferior vena cava, with extension to the renal veins, thrombosis of the hepatic veins, and cirrhosis of the liver.

At autopsy the abdomen was markedly distended, containing about 12 L. of fluid. The inferior vena cava, the iliac, hypogastric and femoral veins were greatly dilated. Permission to explore vessels in the lower extremities was not granted. From about 5 cm. above the confluence a large, well organized thrombus filled the lumen of the cava. (Fig. 1.) This obstructed but did not occlude the renal veins. The thrombus extended upward to a point 3 cm. above the right renal vein. Here the cava was transformed into a small, cord-like structure with a lumen scarcely 3 mm. across. The orifices of the hepatic veins were lost in this scar tissue. The

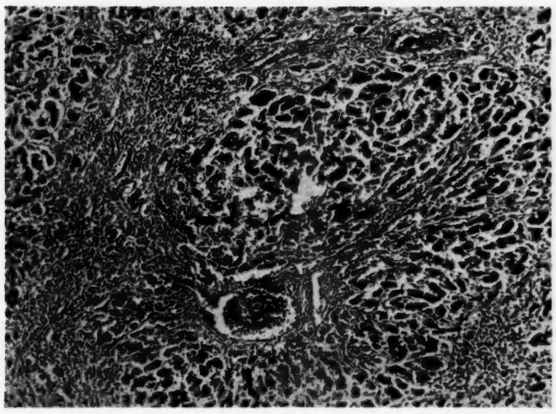

FIG. 2. Liver lobule showing both portal and central cirrhosis. Radially arranged fibrous tissue strands extend from the thick-walled central vein to join the periportal connective tissue bands; hematoxylin and eosin stain, × 153.

cava widened again above the diaphragm but the thoracic portion was also filled with thrombus to the level of the right auricle. The splenic, superior mesenteric and portal veins were dilated and contained thrombi. The liver was enlarged with thickened capsule and rounded edges. The parenchyma was light tan in color and cut with greatly increased resistance. The lobulations were regular. Microscopically, the liver showed both portal and central cirrhosis. (Fig. 2.) Very few central veins remained. Where central veins were patent there were signs of congestion. In other areas in which the veins were obliterated there was extensive collapse fibrosis. Both the central and portal veins were thick-walled and dilated. Except in a few areas the liver cords were not distorted and the hepatic cells were normal. Large engorged venous channels coursed beneath the thickened capsule of the liver. The veins in the round ligament were dilated and many contained thrombi. The umbilical vein was patent. The spleen was greatly enlarged. The parenchyma was dark red and extremely friable. The Malpighian bodies were difficult to distinguish. Microscopically, the spleen showed many epithelioid tubercles with caseating centers. The gastrointestinal tract showed esophageal varices, extensive mucosal erosions of the stomach and hemorrhoids.

In the chest there were old fibrous adhesions covering both lungs. The pleural surfaces were studded with tiny, raised, firm, white tubercles. The lungs were heavy, containing bloody, frothy material but were not consolidated. Microscopically, there were recanalized thrombi in

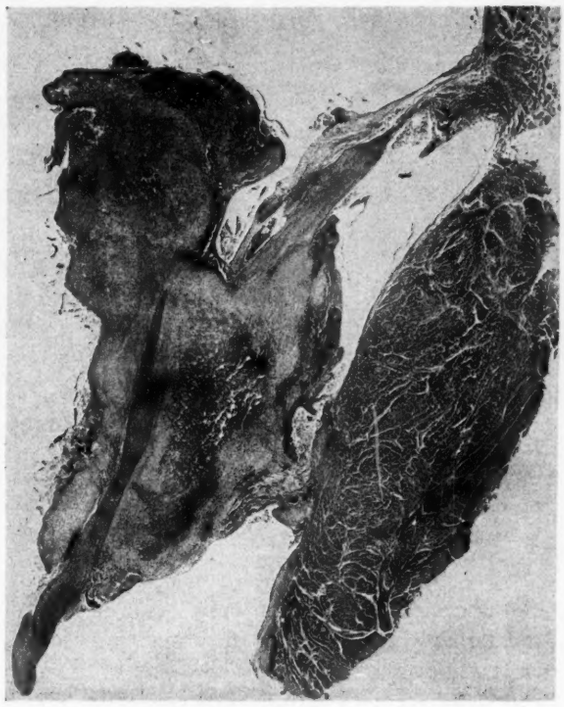

FIG. 3. Mitral valve showing left auricle; deformed valve leaflet with vegetation which is adherent to the endocardium of the left ventricle; hematoxylin and eosin stain, × 7.

many pulmonary arteries and arterioles. In the heart the mitral and aortic valves were distorted by the presence of large, well organized, white vegetations which extended from the line of closure along the chordae tendineae to the papillary muscles. (Fig. 3.) Microscopically, the vegetations were partially hyalinized but covered by a layer of fresh fibrin. No bacteria could be demonstrated. Throughout the myocardium several coronary veins contained thrombi or had recanalized lumens. There was no evidence of rheumatic carditis.

The kidneys appeared normal grossly. Microscopically, many glomeruli had thickened basement membranes, some severe enough to be classified as wire-loop lesions (Fig. 4.) A few glomeruli were partially hyalinized and some were completely obliterated by hyaline. Many Bowman's capsules were thickened but there were few crescents. The tubular epithelium was swollen and granular. The lumens contained occasional hyaline and granular casts. The venules were dilated. There was generalized enlargement of the thoracic and abdominal lymph nodes. They were congested and on section showed numerous small, caseating tubercles. Microscopically, there were many epitheli-

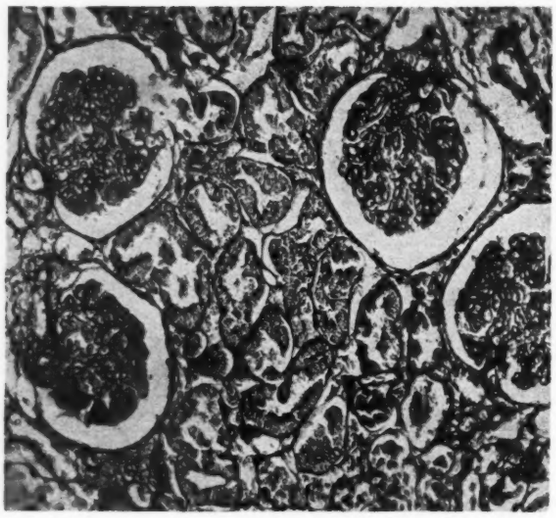

FIG. 4. A group of glomeruli with thickened basement membranes; azan carmine stain, × 220.

oid tubercles with giant cells and caseation. Acid-fast stains showed a few acid-fast bacilli in the abdominal nodes.

The anatomic diagnoses were multiple venous thromboses, atresia of the inferior vena cava due to thrombosis, thrombosis of the hepatic veins, thrombosis of the portal vein, portal and central cirrhosis of the liver, chronic passive congestion of the spleen, esophageal varices, vegetative endocarditis, mitral and aortic valves, chronic intercapillary glomerulonephritis, multiple erosions of the stomach, tuberculous pleurisy, inactive, and tuberculosis of the spleen, thoracic and abdominal lymph nodes.

COMMENT

This patient presented several pathologic processes which may be discussed under the headings of (1) local processes, primarily the result of particular thromboses, and (2) general disease, the cause of the thrombosing tendency. The course and interpretations are summarized in Figure 5.

Chiari's syndrome: In 1946 the patient presented the typical clinical picture of abdominal pain, enlargement of the liver and ascites. Later other manifestations of portal hypertension developed, namely, splenomegaly, esophageal varices and hemorrhoids. The Chiari's syndrome was of the less common, slowly developing type appearing over a period of at least a month. During the latter part of 1947 he lost his ascites and was subjectively well. The collateral circulation had apparently compensated for the hepatic vein block.

Inferior Vena Cava Thrombosis: The clinical evidence for this consisted of the superficial abdominal collateral circulation. Peripheral edema is not seen in inferior caval obstruction unless the leg veins are involved nor is ascites present without concomitant obstruction of the hepatic veins.[6] The collateral circulation beginning in the groin, with blood flowing upward into the axilla,

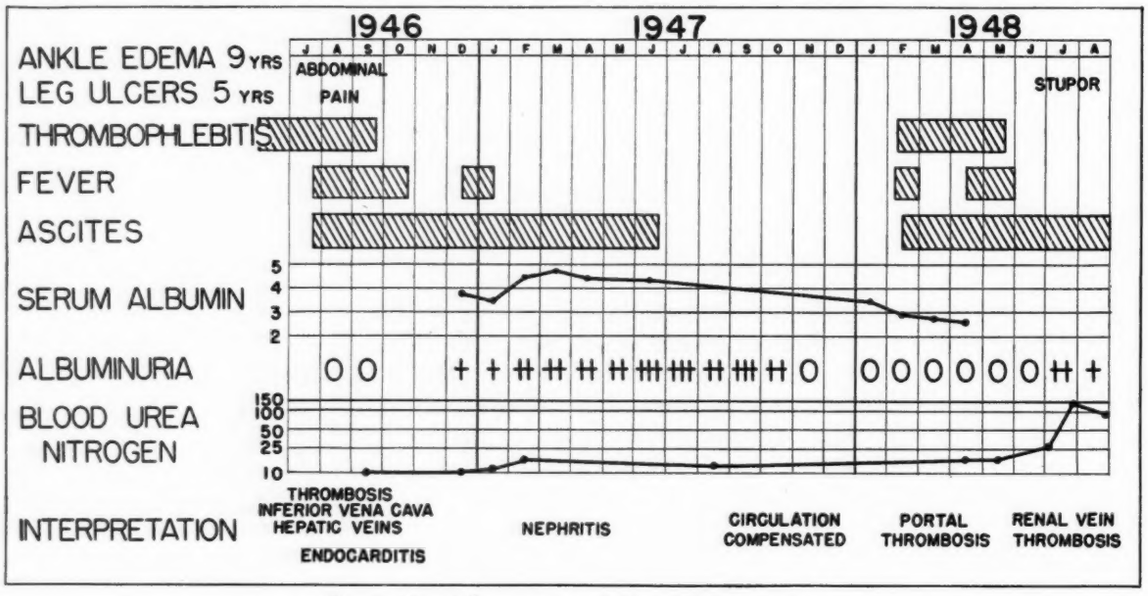

FIG. 5. Graphic summary of the patient's course.

is typical of inferior vena cava block. This patient did not present the typical caput medusa of portal hypertension, with centrifugal blood flow from the umbilical veins, although he did have portal system obstruction. Inferior vena caval obstruction was present in 21 per cent of Thompson's cases of Chiari's syndrome.

Portal Thrombosis: At autopsy thromboses of the portal, splenic and superior mesenteric veins of fairly recent origin were encountered. In Thompson's series this was seen occasionally as a terminal event. In this case the portal vein obstruction probably started six months before death when the ascites recurred.

Renal Vein Thrombosis: It was suspected clinically that the episode of stupor and back pain, with nitrogen retention, oliguria, albuminuria and hematuria a month before death, might represent a progression of the caval thrombosis to involve the renal veins. At autopsy the patient did indeed have a partial obstruction of the renal veins due to fresh inferior caval thrombosis.

Endocarditis: On the patient's first hospital admission in 1946 he had a high fever, heart murmurs which changed, anemia and a suggestive small embolism. Bacterial endocarditis was suspected but later discounted. At autopsy thrombotic vegetations with fibrin deposits on the surfaces were present on the mitral and aortic valves. The type of endocarditis could not be determined pathologically. It was not the type seen in disseminated lupus erythematosus in which the lesions begin as fibrinoid degeneration within the valve tissue and usually do not ulcerate.[7] The lesions were not typical of rheumatic valvulitis. Although no bacteria could be demonstrated in the vegetations, it seems most likely that they represented a healed bacterial endocarditis. The clinical course suggests this interpretation. The patient had chronic leg ulcers for a long time which certainly gave occasional bacteremia with ample opportunity for valvular implantation. Although he had no evidence of antecedent valvular damage, about 50 per cent of the cases of subacute bacterial endocarditis do not show previous valve damage.[8]

Cirrhosis: Pathologically, the liver showed a combined central and portal cirrhosis. The lesion in the central areas is explained by the hepatic vein occlusion. The portal fibrosis might be a Laennec's type. The patient was a spree drinker but his diet was generally adequate. It is a general impression that periodic alcoholics do not get cirrhosis as frequently as do continuous drinkers. The hepatic cells appeared surprisingly healthy with none of the degenerative changes often seen in Laennec's cirrhosis. It is possible that the portal fibrosis was secondary to the portal vein thrombosis.

Nephritis: In 1947 albuminuria developed which persisted most of that year. This was accompanied by a few white cells but only occasionally by red cells and casts. There was also a slight, perhaps insignificant, rise in the blood urea nitrogen at this time. Obstruction of the inferior vena cava above the renal veins can produce albuminuria if it occurs suddenly enough.[6] This patient's occlusion probably developed rather slowly. Moreover, the albuminuria did not appear until some months after the occlusion began. Active endocarditis is frequently accompanied by focal embolic glomerulonephritis occasionally by the diffuse type. Baehr[9] has pointed out that in healed bacterial endocarditis one-third of the cases present diffuse glomerulonephritis. In this patient evidence of nephritis appeared only after the endocarditis had healed. Pathologically, the kidney lesion was a diffuse glomerulonephritis. It was predominantly of the intercapillary type in contrast to the extracapillary type associated with crescent formation. This nephritis was probably associated with the healed endocarditis and adequately explains the albuminuria seen during 1947. However, the nephritis was not of sufficient severity to account for the terminal uremia which was undoubtedly due to the renal vein thrombosis.

Tuberculosis: At autopsy there was old tuberculosis of the pleura with active lesions

in the thoracic and abdominal lymph nodes and spleen. This was apparently a terminal event.

The underlying disease in this case was apparently a recurrent idiopathic thrombophlebitis.* The patient did not have any of the diseases commonly associated with venous thrombosis, namely, cancer, prior infection, arteriosclerosis or rheumatic heart disease.[10] Polycythemia, an occasional cause of multiple thromboses,[3] was not present nor was thromboangiitis obliterans, which is sometimes accompanied by a migratory phlebitis. The coagulability of the blood was not increased. Baehr, Klemperer and Schifrin[11] have described a syndrome of acute febrile anemia and thrombocytopenic purpura with widespread platelet thromboses. In this syndrome the platelets are low and the capillary fragility is increased as in the patient here presented. However, previous cases have all been in females, the course has been very short and there has been considerable bleeding; while pathologically, the thromboses are composed entirely of platelets and are present in the arterioles and capillaries, not in the veins. None of these factors were present in this patient. The combination of endocarditis and nephritis suggests disseminated lupus erythematosus.[7] The wire-loop glomerular capillaries are seen typically in this disease. However, the patient had no skin rash, pericarditis or pleuritis. The endocarditis did not present the typical lesions described in this disease nor was there pathologic evidence of widespread collagen degeneration. Onion-skin arterioles were not found in the spleen.

SUMMARY

A case is presented of a young man who had thrombophlebitis of the legs for many years. At twenty-four years of age thrombosis of the inferior vena cava suddenly developed involving the hepatic veins with the typical symptomatology of Chiari's syndrome. This disease process was complicated by a concurrent endocarditis which responded to penicillin therapy. Six months after the development of the caval thrombosis he began to show evidence of what proved to be chronic glomerulonephritis. A year after the caval thrombosis the patient's collateral circulation had compensated sufficiently so that the ascites and edema disappeared. After a six-month interval the ascites reappeared due to the development of a portal vein thrombosis. Two years after the first appearance of the caval thrombosis the patient died in uremia following the extension of the thrombosis to the renal veins.

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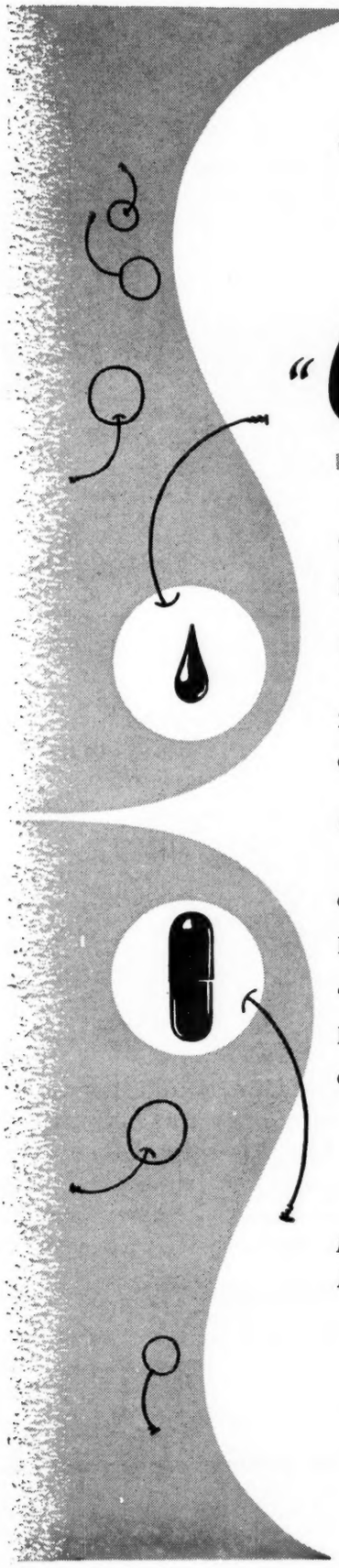
* A series of six cases of multiple venous thromboses, some similar to this case, has recently been reported. (Gerber, I. E. and Mendlowitz, M. *Ann. Int. Med.*, 30: 560, 1949.)



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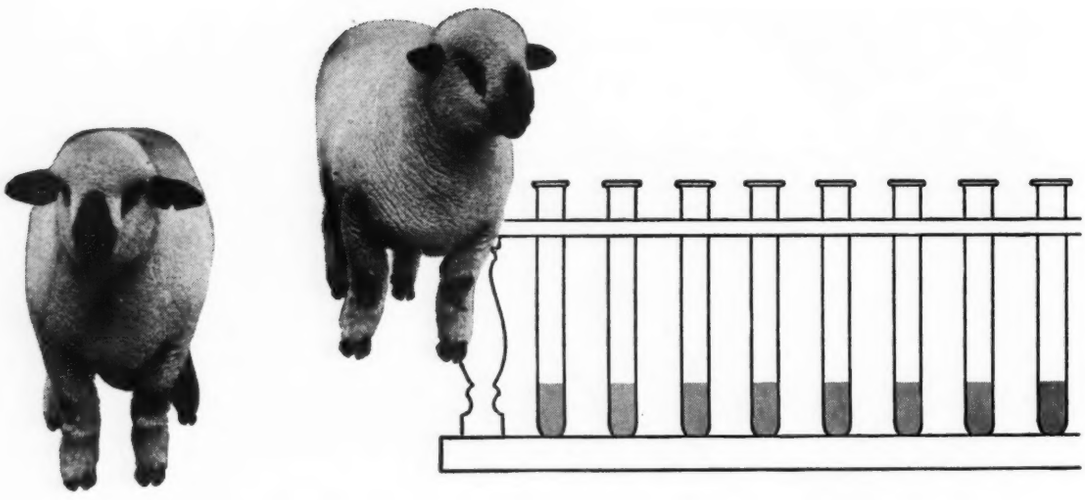

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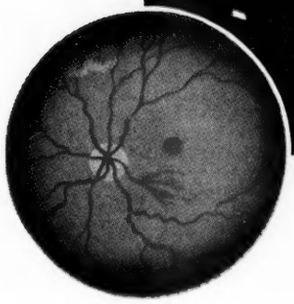
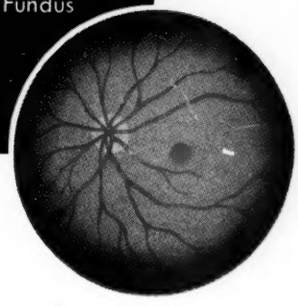


Normal Ocular Fundus



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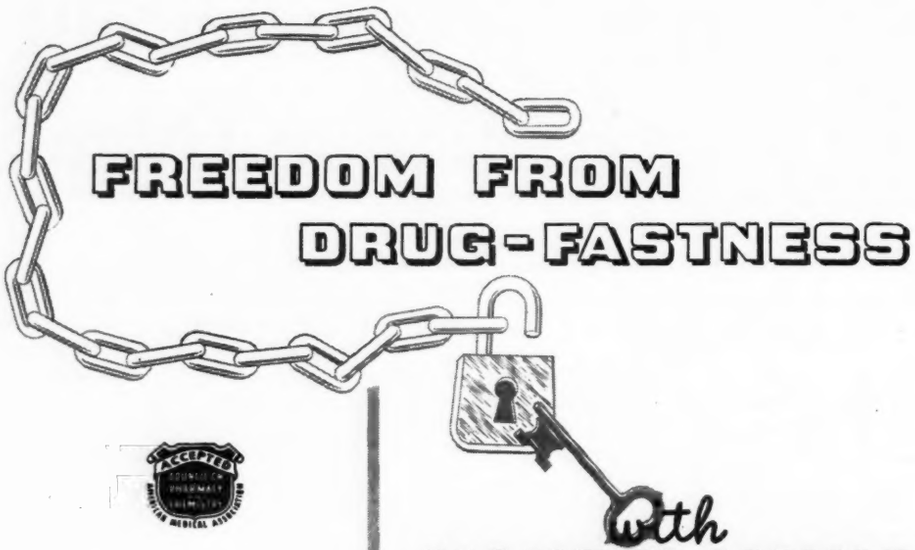

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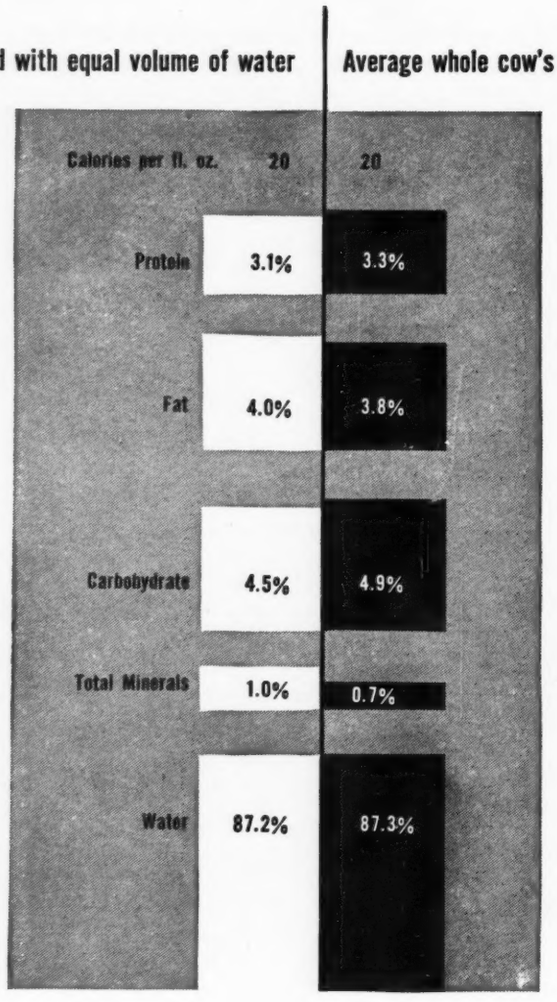

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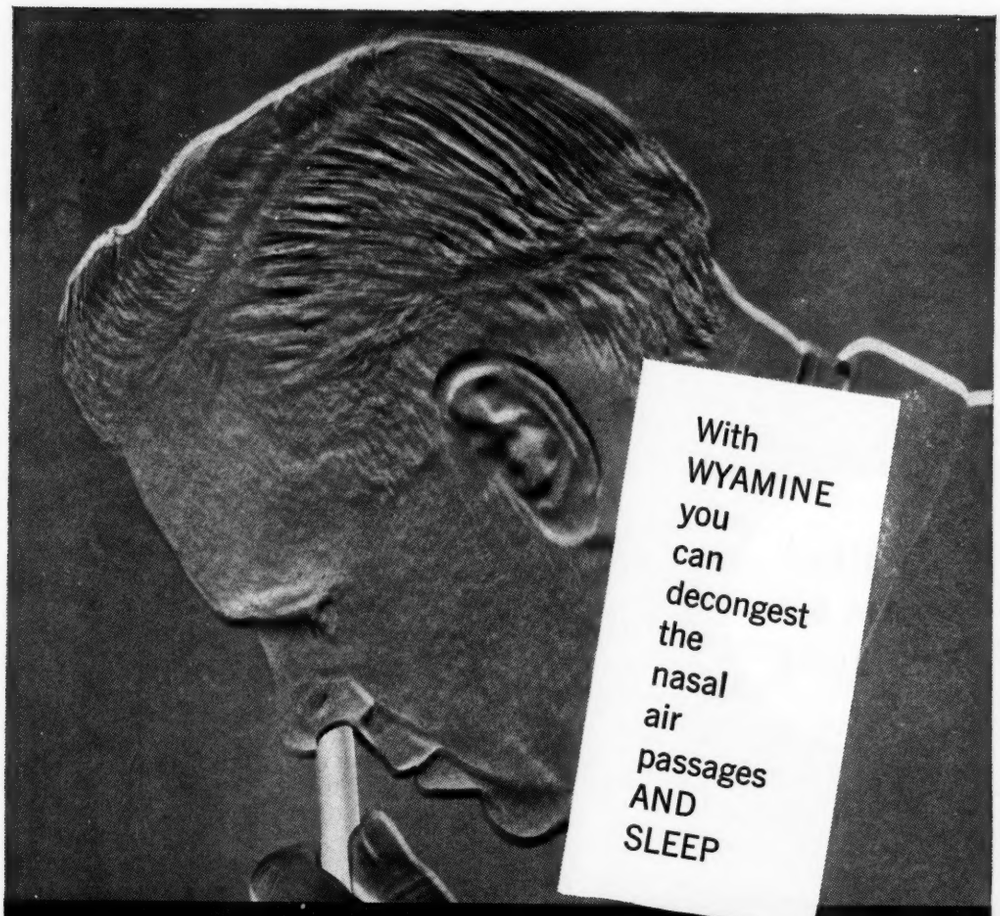

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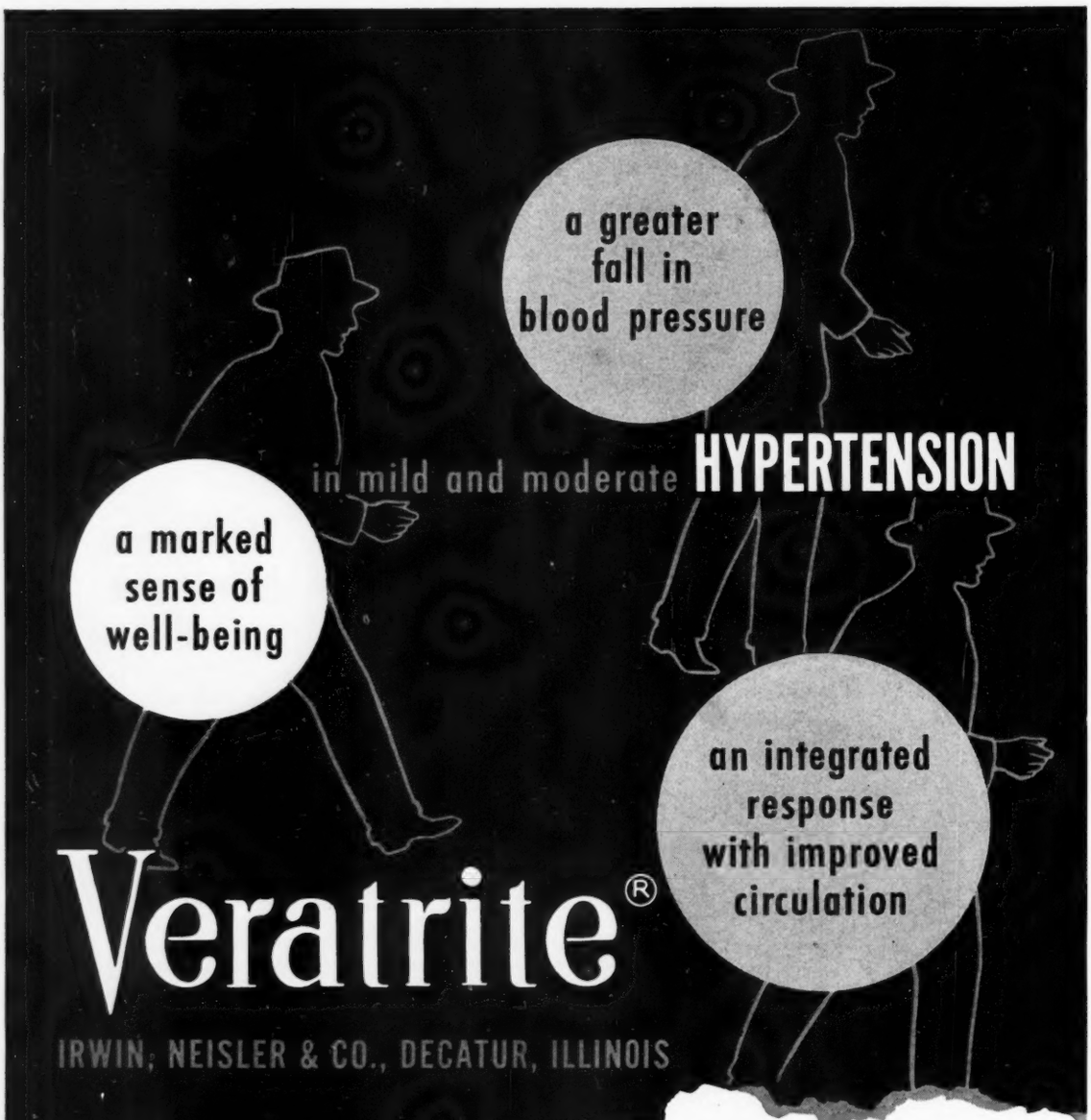

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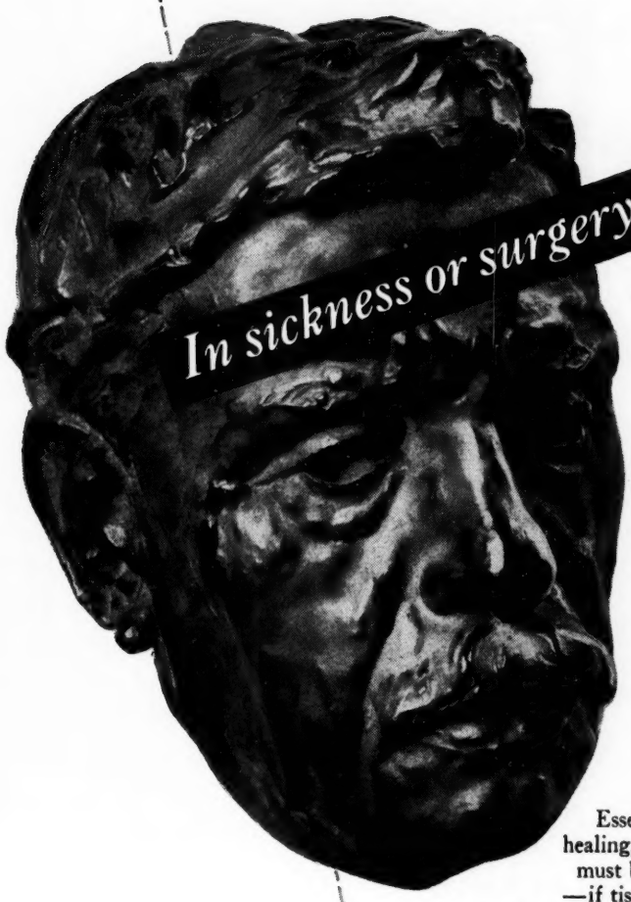

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"Saturation Dosage"

of vitamins b *and* c

Depletion of the critical water-soluble B complex and C vitamins occurs so commonly in the presence of physical pathology, as to make a presumption of nutritive impairment[2] almost axiomatic. Essential to normal cell metabolism and wound healing, these poorly-stored, readily-diffusible factors must be replenished — usually by *massive dosage* —if tissue rehabilitation[3] and return to health[4] are to be expedited. • Allbee with C 'Robins' provides this all-important "saturation dosage" in convenient capsule form. It incorporates the important B factors in 2 to 15 times daily requirements, plus 250 mg. of vitamin C — *the highest strength of ascorbic acid available today in a multi-vitamin capsule.* • Its prescription represents a sound contribution toward decisive recovery from disease, or toward pre- and post-operative nutritional support.[1]

A. H. ROBINS CO., INC. · RICHMOND 20, VA.
Ethical Pharmaceuticals of Merit since 1878

FORMULA: *Each Allbee with C capsule contains:*

Thiamine hydrochloride (B_1)	15 mg.
Riboflavin (B_2)	10 mg.
Nicotinamide	50 mg.
Calcium pantothenate	10 mg.
Ascorbic acid (C)	250 mg.

REFERENCES: 1. Coller, F. A. and DeWeese, M. S.: Preoperative and Postoperative Care, J.A.M.A., 141:641, 1949. 2. Jolliffe, N. and Smith, J. J.: Med. Clin. North America, 27:567, 1943. 3. Kruse, H. D.: Proc. Conf. Convalescent Care, New York Acad. Med., 1940. 4. Spies, T. D.: Med. Clin. North America, 27:273, 1943.

allbee® WITH C

Robins

"just a few pounds" **overweight**

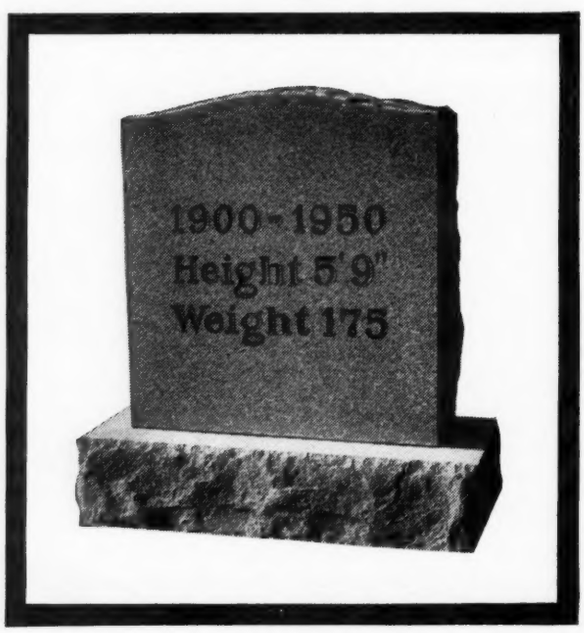
How wrong the patient is who shrugs off "a few pounds" of overweight as something of little consequence!
As every physician knows, those "few pounds" overweight may put that patient "a few feet underground" before his time.
Weight reduction—of even a few pounds—is often the surest means of lengthening life and diminishing future illnesses.
Smith, Kline & French Laboratories, Philadelphia

Dexedrine* Sulfate

The most effective drug for control of appetite in weight reduction

tablets

elixir



*T.M. Reg. U.S. Pat. Off. for dextro-amphetamine sulfate, S.K.F.

For quick relief

of joint and muscle pain

Sufferers from fibrositic disorders (e.g., muscular rheumatism, myalgia, lumbago, pleurodynia, synovitis, bursitis, neuralgia, sciatica, etc.) obtain quick and long-lasting relief with

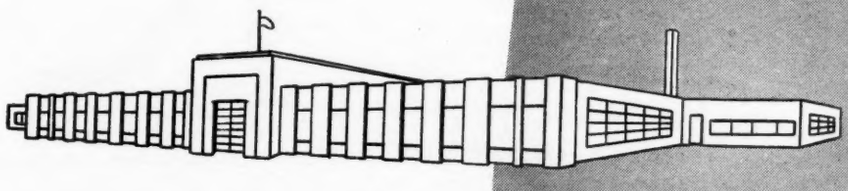
ARTHRALGEN®

arthralgesic unguent

Pain and discomfort in joints, muscles, tendons or nerve sheaths are alleviated, usually in a matter of minutes. Aching and stiffness are replaced by a comfortable sensation of deep warmth and relaxation. With the concomitant use of moist or dry heat, the Arthralgen effect lasts for as long as six hours.

Arthralgen's special ointment base permits quick penetration of the active ingredients: methacholine chloride for deep vasodilation; methyl salicylate for analgesia; and menthol and thymol for rubefaction. Action is quick; relief is prompt and lasting.

Arthralgen is available in 1 ounce tubes and half-pound jars.



Whittier
LABORATORIES
Division Nutrition Research Laboratories • Chicago 30, Illinois

in Mixed Bacterial Genitourinary Infections

Aureomycin is now rapidly becoming recognized as a drug of choice in the treatment of mixed bacterial genitourinary infections, particularly those in which *Escherichia coli* and *Aerobacter aerogenes* play a part. Intractability of a genitourinary infection is an especial indication for aureomycin.

Aureomycin has also been found highly effective for the control of the following infections: African tick-bite fever, acute amebiasis, bacterial and virus-like infections of the eye, bacteroides septicemia, boutonneuse fever, acute brucellosis, Gram-positive infections (including those caused by streptococci, staphylococci, and pneumococci), Gram-negative infections (including those caused by the *coli-aerogenes* group), granuloma inguinale, *H. influenzae* infections, lymphogranuloma venereum, peritonitis, primary atypical pneumonia, psittacosis (parrot fever), Q fever, rickettsialpox, Rocky Mountain spotted fever, subacute bacterial endocarditis resistant to penicillin, tularemia and typhus.

AUREOMYCIN HYDROCHLORIDE LEDERLE

Capsules: Bottles of 25, 50 mg. each capsule. Bottles of 16, 250 mg. each capsule.
Ophthalmic: Vials of 25 mg. with dropper; solution prepared by adding 5 cc. of distilled water.

AUREO-MYCIN

LEDERLE LABORATORIES DIVISION AMERICAN Cyanamid COMPANY 30 Rockefeller Plaza, New York 20, N.Y.

Advertisers Index

March 1950

Pyribenzamine

For control of allergic symptoms which may accompany a Common Cold . . .

Pyribenzamine hydrochloride has been effectively and widely used in the control of allergic symptoms. Clinical tests have repeatedly shown that Pyribenzamine provides maximum allergic relief with minimal side effects. For relief of the allergic symptoms which may be associated with the common cold, Pyribenzamine is available in the following forms:

1. Pyribenzamine-Ephedrine for systemic treatment

Each tablet contains 25 mg. of Pyribenzamine hydrochloride and 12 mg. of ephedrine sulfate. This combination synergistically promotes decongestion of the entire respiratory tract including the nasopharyngeal mucosa.

2. Pyribenzamine Nebulizer to control nasal symptoms

Immediate relief with no systemic side effects. Pocket-size nebulizer distributes a mist of minute droplets of Pyribenzamine hydrochloride Nasal Solution 0.5% throughout the nasal passages.

3. Pyribenzamine Expectorant to control cough

Each teaspoonful contains 30 mg. of Pyribenzamine citrate, 10 mg. of ephedrine sulfate and 80 mg. of ammonium chloride. Highly effective for relief of cough. Blocks congestive and spasmogenic effects of histamine, shrinks respiratory mucosa and liquefies bronchial secretions.

More prescriptions have been written for Pyribenzamine than for all other antihistaminics.

Ciba PHARMACEUTICAL PRODUCTS, INC., SUMMIT, NEW JERSEY

PYRIBENZAMINE (brand of tripelennamine) Trade Mark Reg. U. S. Pat. Off. 8/162288